at

ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGIC EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

57TH MEETING

Friday, December 12, 1997

8:10 a.m.

Doubletree Hotel

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

at

Plaza I, II and III
1750 Rockville Pike
Rockville, Maryland 20852

at

PARTICIPANTS

Blaine F. Hollinger, M.D., Chairperson
Linda A. Smallwood, Ph.D., Executive Secretary

MEMBERS

Jerry A. Holmberg, Ph.D.
Rima F. Khabbaz, M.D.
Jeanne V. Linden, M.D.
William J. Martone, M.D.
Kenrad E. Nelson, M.D.
Joel I. Verter, Ph.D.

TEMPORARY VOTING MEMBERS

John M. Boyle, Ph.D.
Norig Ellison, M.D.
Margaret A. Kadree, M.D.
Chris W. Mathews, M.D.
Paul R. McCurdy, M.D.
Mark A. Mitchell, M.D.
David F. Stroncek, M.D.

NON-VOTING CONSULTANT

David W. Gates (Industry Representative)
Katherine E. Knowles (Consumer Representative)

at

C O N T E N T S

at

P R O C E E D I N G S

Introductory Remarks

DR. SMALLWOOD: Good morning and welcome to the second day of the 56th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

Yesterday, I read the conflict of interest statement that applies to this meeting. That statement applies to today's proceedings as well. In addition, I would like to announce that we have additional individuals that will be serving with the committee today. Those that are here, I would like to introduce them.

Dr. Chris Mathews, would you please raise your hand? Dr. Mathews is a member of the Antiviral Committee, the Center for Drugs. We also have Dr. David Gates who is a member of the Microbiology Panel, the Center for Devices. We will also have Dr. Margaret Kadree joining us, hopefully, for this discussion as well. She is a member of the Microbiology Panel at the Center for Devices.

For those of you who were not here yesterday, I would just like to introduce our newly appointed Committee Chair. You may be familiar with him, but Dr. Blaine Hollinger has just been appointed as our new chair.

In the interest of fairness, I will go around and

at

introduce our committee members again; Dr. Rima Khabbaz, Dr. Joel Verter, Dr. Jerry Holmberg, Dr. Norig Ellison, Dr. Mark Mitchell, Dr. John Boyle, Dr. Jeanne Linden, Dr. David Stroncek, Ms. Katherine Knowles. I think those are all of our members.

I would just like to let you know that Ms. Katherine Knowles is our non-voting consumer representative and Dr. David Gates is our non-voting industry representative. They are present for this morning's session.

The first session, the committee will be sitting as a medical-device panel for our discussion this morning. If there are any declarations to be made with respect to conflict of interest, I would ask that anyone do that now before we proceed. If not, then I will turn the proceedings of this meeting over to our chairman, Dr. Hollinger.

Thank you.

DR. HOLLINGER: Thank you, Dr. Smallwood and good morning. We have two sessions today. This morning is going to be on in-vitro diagnostic detection of HIV viral load. This afternoon, there will be a session, an informational presentation, primarily, on HCV risk in sexual partners.

So we will start this morning's session. Dr. Dayton will present background and introduction to this

at

issue.

Dr. Dayton?

TOPIC II

IN VITRO DIAGNOSTIC DETECTION OF HIV VIRAL LOAD

Background and Introduction

DR. DAYTON: Good morning.

[Slide.]

The topic is a patient-management claim for the Roche HIV Amplicor Monitor Assay. The issue is should the FDA allow a patient-management claim for the Roche Amplicor Monitor Assay which is currently licensed for a prognostic claim.

Let me give you some background and remind you of the last time we saw this product come before this committee when we first licensed it. At the previous meeting of the Blood Products Advisory Committee devoted to considering the issue of HIV viral-load testing for prognosis and patient management, the agency discussed the concept of three hierarchical potential claims for viral-load assays; prognosis, monitoring and management.

I have just put up here a little cartoon schematic to illustrate how we, at that time, have been distinguishing amongst those three possible claims.

at

In prognosis, you would take one or so measurements at baseline and they would have predictive value for the eventual clinical outcome. The next level up in the hierarchy we have been calling monitoring. That would be interpreted as you make sequential measurements under therapy and each of those measurements has predictive value over and above the predictive value of the baseline measurement.

The Rolls Royce of claims, of course, would be of a full-blown management claim which is schematized down here. The idea study for that, and it is hard with this disease and in this day and age, to get ideal study, but the ideal study would involve some kind of treatment regimen, a measurement with the viral load assay, the viral RNA assay, and then a clinical decision made on that measurement to either go to this therapy or that therapy or discontinue therapy, whatever, and then sequential measurements to see how you are doing.

All of those should have predictive value towards the eventual clinical outcome.

As you remember, there was considerable discussion and, really, very astute discussion, as to whether or not monitoring and management, these two claims here, could ever be disassociated in the real world of the clinic.

at

Obviously, the main reason for monitoring is to determine whether or not to discontinue or switch treatments.

Even if it were not the main reason, the lure of basing clinical decisions on viral-load changes during therapy would be irresistible.

So, at one level, the idea of a separate monitoring claim might have some attraction because, if you couldn't base management decisions on it, at least you could tell the patient, "Well, you are doing better," or, "You are not doing better."

But, as was very astutely discussed, in the real world of the clinic, a monitoring situation is really a management situation. However, I don't think this was absolutely etched in stone and it may be a topic for further discussion.

[Slide.]

This is the claim that they would like to go for. The test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1-infected patients. The test can be used to assess patient prognosis by antiretroviral therapy by serial management of plasma HIV-1 RNA levels during the course of antiretroviral treatment.

at

[Slide.]

What I am going to present to you now is a short talk to organize your thinking and prepare you for what is coming next. After me, the sponsor will present a very detailed description of their studies and then our own statistician, Paul Flyer, will go into the details of the statistics later on.

In this case, the statistics is everything. Remember that this kit is already licensed for a prognosis claim and we are now questioning whether we should upgrade that to a management claim.

In this study, the intent-to-treat population--this was study NV14256. This was basically the only study included in the submission. The study was the intent-to-treat population of 970 patients. All of them had been on prior zidovudine. Most of them had been on zidovudine treatment for over a year and they were discontinued either because they couldn't take zidovudine or they weren't responding to it.

At the entry to this study, the patients were put on either one of three protocols, ddC, saquinavir or saquinavir plus ddC.

Now, this is sort of a hybrid or an intermediate between the types of studies I originally displayed. What

at

the analysis is going to claim or report is that making sequential RNA measurements after switching to these therapies has additional prognostic value over the baseline measurements alone. The import of that finding would say that, therefore, it makes sense to continue to sequentially monitor RNA levels during therapy.

What is missing from this, and I think this will be an interesting topic for debate, is a clinical decision that is based upon this assay measurement. We may elect to go without that. I am sure that you will want to discuss that.

There is a switch involved here from this initial treatment to the next treatment so we sort of have a little bit of what we were looking for in the Rolls Royce management type claim. Then, after the switch, of course, you go to these three therapies and measure sequential RNA measurements throughout.

Essentially, the study design, then, addresses what we would have called a claim for monitoring and it asks the question, as I just pointed out, of whether sequential RNA monitoring adds prognostic value to the baseline determinations. As I just pointed out, it does not address the efficacy of basing clinical decisions on assay results nor does it demonstrate that viral rebound is associated

at

with resistance, for instance.

But, as I said, it involves at least one switch, so there is a lot here that is worth looking at.

[Slide.]

This lists some of the caveats that I want you to be thinking about as you see the subsequent detailed presentations. Variability--here, I have quoted it as approximately 0.3 logs. To be outside of two standards deviations, you really should be at 0.5 logs so that you really don't want to interpret anything less than 0.5 logs because of the background variability. So the minimal interpretable change is, thus, around 0.5 logs.

The hazard ratios that are generally quoted are for a ten-fold change in RNA levels. Unfortunately, most of the data involves changes smaller than tenfold changes so you have a very narrow range of data to cover the use of this kit.

Another consideration is that it is not enough to show that sequential RNA measurements continue to be prognostic. It is essential to show that they continue to have prognostic value at least partially independent of the baseline values. So, in much of the data that was presented, you see these great-looking Kaplan-Meier plots based on changes in RNA well into the last treatment

at

protocols.

But if that is not doing any better than baseline, then why make sequential measurements. Our statistician will address this issue and I know that the sponsor will address this issue.

Another consideration here is the necessity versus the danger of retrospective analysis. We pretty much realize that, given this disease and given the fast-moving pace of this field in terms of treatment protocols, it is pretty much necessary, in these situations, to go back and do retrospective studies on previously-acquired cohorts.

This automatically gets you into the problem of retrospective wisdom. The cruel term among statisticians is data dredging. I think that we realize that we have to live with a certain amount of this but, perhaps, the way to approach it is to require higher statistical standards than we might require for a prima facia, a priori, approach.

Finally, the last caveat here; what do you tell the physician and what does the physician tell the patient? I think what is absolutely critical here, and it certainly was in the spirit of how the committee focussed its last debate, is what happens when you get to the clinic.

This is a two-edged sword. It may make it easier

at

to get a management claim, which is good, but it may make it harder to decide if there actually is value in the data that is going to be presented to the physician.

All I am really getting at it is not enough to have statistically significant results if the clinical implications are trivial. To make a very simplified description of that, you might very well be in a situation where you can say that, based on your results, this patient, instead of falling in category A now falls in category B with 99.99 percent certainty.

But, if category A is 25 percent of acquiring an AIDS-defined event and category B is 26 percent, who cares? I am not saying that the assay falls down on this. In fact, we have been discussing with the sponsor, and I think they have reasonable data on this. I encourage you to pay close attention to how this question is addressed in the submission.

At this time, I have two questions. Should I read them for the committee or should I wait until later on?

DR. HOLLINGER: Go ahead.

DR. DAYTON: I am hoping today's questions will be comparatively simple although you are certainly welcome to rewrite them.

Should the FDA approve labeling of the Roche

at

Amplicor Monitor Test Kit as an aid in management of patients on antiretroviral therapy for HIV disease? If not, then what additional claim, if any, is appropriate for the Roche Amplicor Monitor based on the current submission?

With that, I will sign off. Thank you.

DR. HOLLINGER: Thank you, Dr. Dayton.

The next presentations are going to be by the sponsor. Mr. Alex Wesolowski will initiate this.

Presentation by the Sponsor

Description of the NV14256 Study

MR. WESOLOWSKI: Good morning. My name is Alex Wesolowski. I am senior director of regulatory and clinical affairs at Roche Molecular Systems. On behalf of Roche Molecular Systems, I would like to welcome you all to this morning's session.

I think Dr. Dayton outlined some of the important issues before us today. I would like to begin with some opening remarks and then I will touch on the presentations that we will be doing over the course of the morning.

Firstly, I would like to review some of the events that have transpired. On June 3, 1996, the FDA approved the Amplicor HIV-1 Monitor test for use in prognosis of patients for disease progression. At that time, the agency asked us to do post-approval studies comparing HIV-1 RNA levels to

at

clinical endpoints in support of therapeutic monitoring in patient-management claims patient-management claims.

It was believed, as a result of the previous panel meeting, that clinical endpoint studies were the most appropriate comparators to us in order to analyze these data. As a result of those requirements, we, of course, are involved now in a number of studies. They are ongoing. They are, as you might expect, in some cases, difficult studies to perform. They take a long time to get the data but they are, indeed, under way.

One of the other things that has transpired from the time that our test was first approved has been that combination therapy approaches to HIV infection has resulted in dramatic reductions in HIV-1 RNA levels, especially with the availability of protease inhibitors. This is something I think that has been well-documented in technical publication.

Just as a little bit more of a background, in July of this year, the Center for Drug Evaluation and Research Antiviral Drug Advisory Panel recommended that HIV-1 RNA levels actually be used as a primary endpoint for drug clinical studies replacing clinical endpoints. I think was a dramatic but appropriate development in drug clinical studies.

at

Also, in November, just recently, the Department of Health and Human Services Panel on Clinical Practices for the treatment of HIV infection released a guideline for the use of antiretroviral agents. In the guideline, it clearly states that viral-load testing is the essential parameter in decisions to initiate or change antiretroviral therapy.

That document also contains suggested ways to use HIV-1 RNA to make those there decisions.

I think it is fair to sum all of this up by saying that the current goal for antiretroviral drug therapy of HIV-infected individuals it achieve dural viral suppression as measured by HIV-1 RNA.

[Slide.]

I think, as a combination of some of these things that we just discussed, clearly, we don't have clinical endpoint trials anymore. The changes we see in HIV-1 RNA levels now and the reduced number of endpoints and, indeed, the fact that most studies are not taken to clinical endpoint heightens the importance of some of the historical studies.

I guess, in this case, we are talking about history going back only about two or three years, but, clearly, it serves to show how valuable some of the earlier antiretroviral studies were because they do have clinical

at

endpoints and, for the purposes of analyzing data, certainly for a diagnostic test or a monitoring tool, the availability of clinical endpoints is nearly essential.

I point this out just to bring to your attention the fact that we did choose to use a clinical study that was run by Hoffman LaRoche for the drug saquinavir. It was a very large, very well-organized study, had a large number of clinical endpoints. The study did use the Amplicor HIV-1 monitor test and the data were readily available to us.

So it seemed to be the appropriate selection for a number of reasons, some of the reasons pointed out by Dr. Dayton a little bit earlier today.

Importantly, the case here is that we do need a significant number of AIDS-defining events in order to reach a level of statistical significance. Current studies under way, as I said before, do not go to clinical endpoints so there is no comparison to AIDS-defining events, leaving us with a situation where we are really only looking at decreased levels of RNA or increases in CD4. It is tough to make the statistical cases when the studies are run that way.

[Slide.]

This is a slide containing our proposed intended-use statement. Dr. Dayton reviewed that earlier

at

today. Importantly, the revisions in this proposed intended-use statement would be that the test be used to manage patients not only by doing initial prognosis but, also, by monitoring the effects of antiretroviral therapy.

We believe strongly that the combination of those two, just in and of itself, is clinical management of the patient.

[Slide.]

I would like, now, just to review briefly, our agenda for this morning. First, we are going to ask Dr. Miklos Salgo who is the director of clinical virology research at Hoffman-LaRoche, and he was the head of the team that performed the NV14256 study, to give us a brief description of that.

We will follow that with the presentation of the statistical analyses of those study data which are presented in our PMA application and that will be done by Dr. Michael Miller who is a statistical consultant to Roche Molecular Systems.

Following Dr. Miller's presentation, we are going to ask Dr. Salgo to review some of the clinical conclusions from our data analyses from that study.

We have also invited today Dr. Richard Haubrich from the University of California at San Diego to do a

at

presentation at the open session of this meeting. That will be right after the break, I believe. Dr. Haubrich will be discussing a study that we are, in part, sponsoring. It is the CCTG570 study which is a patient management study using RNA.

It is important to note that the data that Dr. Haubrich will be discussing do not appear in our submission. However, we believe that they are important enough that they should be presented and understood by this panel.

We are also very happy to say that we have Dr. Allen McCutchan from the University of California, San Diego, and Dr. Haubrich will be available to answer questions about viral-load testing on our behalf. So they will be available to answer any questions you may have.

With that, I would like to turn the podium over to Dr. Salgo for a description of the saquinavir NV14256 study.

Description of the NV14256 Study

DR. SALGO: Good morning.

[Slide.]

First of all, I would like to address the issue of why are we looking at this study today. This was a presentation basically that was presented about a year and a half ago at Vancouver and was a clinical-endpoint study that was instrumental in the approval of Invirase.

at

The reasons we are looking at it today are several. First of all, it was a large clinical-endpoint study and, secondly, it was one of the first studies where HIV-1 RNA was measured at regular intervals throughout the study in all patients. Obviously, there have been a number of other studies that has also been done on.

But this combination of the clinical endpoints and the frequent viral-load monitoring allows us to make some interesting observations about the prognostic value of serial measurement of HIV RNA.

As Dr. Dayton mentioned, this study is not a patient-management study or a treatment-strategy study. Mainly, at the time, there were very limited other treatments available and that was not the goal of the study. But, as Dr. Wesolowski mentioned, a treatment-strategy study will be described a little later by Dr. Haubrich in a presentation of a study that has just had an interim-analysis done.

[Slide.]

Basically, the NV14256 study was a double-blind, randomized, placebo-controlled study in patients discontinuing zidovudine either because of intolerance or failures. They had no prior ddC or ddI and were randomized either to ddC alone, saquinavir alone or the combination.

at

Keep in mind, of course, that this study was designed a while ago. It was designed, actually, in 1993 at a time way before the documented benefit of combination therapy had come forward.

As you recall, that was ACTG 175 in the Delta study that the results became available towards the tail end of this time period, really, within 1995.

[Slide.]

A surrogate-marker analysis of this study was included in the original RMS filing a while ago. This is the final clinical-endpoint study and, as you can see at the bottom here, it includes what Dr. Miller will be presenting later, some additional analysis by Roche Molecular Systems.

[Slide.]

The study was well-balanced across the baseline demographic characteristics; patients about 38-years old. Here you can see that they are a high viral-load group, about 10^5 or 5 logs, and the CD4 count was quite low, between 160 and 180. They were extensively pretreated with almost 18 months of prior zidovudine therapy.

[Slide.]

Here we can see that they were followed on treatment for almost a year, a little bit more on the combination arm. The follow-up follows them beyond that

at

time almost out to a year and a half.

[Slide.]

Here we can see the RNA changes that occurred over the study and, at the bottom, the number of patients involved. You can see that the combination arm, saquinavir plus ddC, afforded a drop of about 0.5 to 0.6 logs change from baseline. This was maintained in those remaining on study.

In ddC, a less dramatic decline. Saquinavir by itself, less of a decline.

[Slide.]

Here we see the CD4 count increases. Similarly, the combination, saquinavir plus ddC arm, is the best of the three with increases about 36 cells, and that this goes around. But it is maintained above baseline in those remaining on study while the other two arms have a transitory increase.

[Slide.]

Here we see a Kaplan-Meier curve of the time to the first AIDS-defining event or death, ADE as we call it. You can see the number of events here; 88 on ddC, 84 on saquinavir and only 51. This is highly statistically significant by the log rank and, indeed, there is separation of the curves.

at

[Slide.]

Here are the statistics on it and you can see that, using a Cox regression, we have about a 50 percent decline, or 49 percent decline, in the risk of progression to AIDS or death. The two monotherapy arms were not statistically different but, if we compare the combination to saquinavir, as opposed to comparing it to ddC, that comparison was also significant.

[Slide.]

Here we see survival by itself; in other words, time to death. A similar analysis; Kaplan-Meier. Again, the number of events were fewer on combination. Eleven patients died. This, again, was highly statistically significant.

[Slide.]

Here we can see the risk reduction down to 0.32. Similarly, if we compare to saquinavir, also risk reduction. But the two monotherapies are similar and cannot be differentiated.

[Slide.]

So, for the clinical endpoints of the study, we could say that there is a 49 percent decline with combination over ddC, decline in the progression to AIDS or death. With death alone, it was even more dramatic with a

at

68 percent decline. That is a relative risk of 0.32.

[Slide.]

This reiterates that, to a certain extent. In additional analyses that have not been shown here, we looked at how much of the treatment effect--in other words, the 49 percent decline in progression to AIDS or death--could be explained by the surrogate markers and, using the surrogate markers, both of them, RNA and CD4, on treatment, treatment-induced changes, that would explain 61 percent of the analysis.

[Slide.]

Here is the study team. Actually, Dr. Haubrich was a member of the study team and made some of these presentations. Additional members that we thank very much for providing us with this study.

Now we will go on to Dr. Mike Miller with the RMS statistical analysis.

Statistical Analyses of the NV14256

DR. MILLER: Good morning. My name is Mike Miller. I am going to summarize for you the statistical analyses that were done on these data.

[Slide.]

The overall objective of the analysis was first to determine or investigate whether there is prognostic value

at

in continued RNA measurement, and this prognostic value needs to be demonstrated above and beyond the known prognostic value baseline.

We want to, in addition to that, quantify or characterize the strength of this prognostic value or relationship, and that will then tend to support the continued use of the assessment for patient management.

[Slide.]

The study sample is described as before with the three treatment groups from the 256 study. The important thing to remember here is that, in this study, there were protocol-specified regular measurements of RNA and CD4. We started with 970 patients. This worked its way down to 926ÊpatientsÊin the analysis.

Patients were omitted or dropped out from the analysis because their RNA or CD4 readings were not present. So we got, certainly, most of the patients.

[Slide.]

What I want to do now is go through, briefly, what, exactly, was done in the analysis and to give you an idea or a flavor of the calculations but not to get into any great detail about these.

What we did was identify subgroups of the total patient sample; namely, at week 4, week 8, week 16, patients

at

who had survived ADE-free through that particular study week. For each of these patients who had survived ADE-free, we defined the last RNA and the last CD4 assessments at each study week.

These last assessments were as close as possible to the given study week. Whenever an assessment was missing at a given study week, we carried forward the previous assessment as long as it was not a baseline assessment.

[Slide.]

So we are really interested here in looking at the time-to-progression of an ADE. We look at the risk of an ADE as a function of certain independent variables in this study, both the baseline RNA and CD4 assessments and also this last RNA and CD4 assessments.

The primary analysis was pooled, all three groups together but stratified by the three treatment groups. We also had, in the submission, separate analyses for each treatment group.

[Slide.]

In this pooled analysis, we used the Cox proportional hazards model because this was a model that allows us to look at the joint effects of all four of those independent variables on the risk of progression at each of the study weeks. It allowed us to decide or discern whether

at

the last RNA assessment had prognostic value after taking into account the baseline assessments and the other assessment.

The Kaplan-Meier plots and other life tables that were presented were presented for description, to help us understand what is going on. All of the RNA assessment were log-transformed. We make reference particularly to the change from baseline which is the log base 10 of the ratio of the last to the baseline RNA. This is used to help isolate the effect of the last RNA assessment.

[Slide.]

Certain assumptions had to be checked in order to lend credibility to the model that was eventually used. These exploratory analyses; there is a lot of work that needs to be done. We need to check the assumption of proportional hazards. Generally, that assumption was not dramatically violated across the board. There were occasional violations of proportional hazards, but they were isolated and they did not alter the conclusions.

We noted that, among those four variables, there were some strong relationships amongst the independent variables and this would contribute to multicolinearity which means it makes it even more difficult to isolate the effect of one variable given the others.

at

We looked at, in the combined model, whether or not, let's say, the last, or the change from baseline RNA assessment, whether that effect really depended on the treatment group. So we had to check treatment group by covariate interactions.

Again, for the early study weeks, the early cohorts, we did not see any striking or dramatic effect of the treatment groups allows us to make statements about all three treatment groups combined. We did, however, see some treatment-group effects for the later study weeks.

We noted that the Cox model generally is a linear model in the covariates. We even checked departures from linearity. Again, here, we found really no meaningful departures from linearity.

[Slide.]

So, to restate the objectives more specifically, in terms of the models that we have set up, for each of those study-week cohorts, we are going to do a separate analysis to establish the prognostic value of the continued measurement; week 4, week 8, week 16 and so on. Is there any evidence of a relationship between that last RNA value and the risk of progression after adjusting for the other factors.

This will be the statistical significance part.

at

As we heard before, we have to be cautious about an exploratory or retrospective study. Because of the nature of this analysis, there are going to be many repeated analyses. There are going to be a lot of p-values, a lot of statistically significant claims.

We just want to say that we did not adjust for multiple comparisons. That might have been somewhat difficult. But we feel that the strength of the relationships, the consistency of the relationships and the direction of the relationships lend credibility to the whole set of results.

Finally, we want to capture the effect size. What was the size of the effect of the last RNA assessment after adjusting for all that. Is there anything left, anything meaningful left, after we adjust for baseline. So we are going to present something regarding clinical significance.

[Slide.]

So here are all of the cohorts that were used going from week 4 through week 64. Basically, what you have here are the number of patients--for example, at week 16, there, there were 290 patients in the saquinavir group who had actually survived ADE-free through week 16.

We then followed those patients and it turned out that 60 of those patients subsequently developed an ADE

at

sometime during the follow up. So that is what those numbers represent.

As a patient had an ADE at a particular time point, that patient was dropped out of subsequent cohorts. You might wonder why the numbers at week 4 are somewhat lower. You would think that they should be the highest of all. Indeed, they would have been except many of the patients did not have their first RNA or CD4 measurement until after week 4, and so they didn't appear in the week-4 analysis.

[Slide.]

What I would like to do now is just give you some basic descriptions of the effects using the time-to-progression. These are just descriptive statistics. We pick a particular group, the ddC group. We pick a particular time period, starting from study week 16 and then moving forward. These are weeks after week 16. What we did here was simply divide that group up into equal thirds according to the baseline RNA, just to see what effect there might be.

So, roughly speaking, you can think of this group as a group that started out with about 10,000 copies per ml. This group started out with about 100,000 copies per ml. This group started out with about a million copies per ml.

at

As you can see, there is quite a separation here in those groups.

Let's take a look at the same thing where we are doing now, instead of the baseline RNA, the last RNA assessment here. It is not the same three groups, but we are ordering the patients according to the last RNA assessment. Roughly speaking, you can think of 10,000, 100,000, a million, although things have shifted down a bit. By week 16, there has been some treatment-induced reduction in RNA.

Again, we see that there is quite a spread or quite a large difference in those three groups. But, as we have heard earlier, we have to be very cautious about this. We are not going to be claiming that this is, in fact, the effect of the last RNA because much of this separation is probably caused by the baseline, by the baseline RNA.

In order to, at least descriptively, isolate the unique contribution, the unique addition, due to the last RNA assessment, let's go to the third slide.

[Slide.]

We see that now what we have done is that we have ordered the groups, the ddC group, according to the change from baseline, just according to the change from baseline. We see the separation is not as striking, or not as

at

dramatic. In fact, we see that we only get separation really from the last group. You might characterize this as the high-risk group.

This range of change from baselines includes zero, which is really no change from baseline, and, actually, there are many patients who actually increased. This is probably a fair representation of the effect of change at baseline although, even here, we have to caution you that we have not yet fully adjusted for the baseline and, also, the other variables.

So we still have to do some more statistical analysis, although this is somewhat suggestive of the results that we got. I illustrate this for week 16 for ddC. There are many other plots like this for the cohorts for the groups and the groups combined.

[Slide.]

What we have now is a slide with a lot of information. But it is a lot of important information. The reason that we present this slide in its present form is to really show you that we are looking at the repeated measurement of RNA at each of these various study weeks. Separate Cox models were fit for each of these study-week cohorts.

For each Cox model, we have included the baseline.

at

We included the change from baseline. We included baseline CD4. We included the change from baseline in CD4. What we want you to simply note here is that, for each of these study weeks, we were able to demonstrate the statistical significance of the change from baseline in the presence in all of the other factors.

This is of primary importance. The statistical significance was quite striking. The coefficients, themselves, just please notice that they are in the right direction, namely that, for example, being positive here for the change in baseline means that if I have a treatment-induced reduction in RNA, I should then see a corresponding reduction in the risk of progression.

Similarly, if I have a treatment-induced increase in CD4 because that is negative, that should also give me a reduction in the risk of progression.

[Slide.]

So here are study weeks 4, 8, 16, 24, 32. We even go on to study week 40 through study week 64. We see the same kinds of results through study week 40 but then we begin to lose the statistical significance of the change from baseline in RNA and we hypothesize that that is due, perhaps, to the fact that actually the numbers of clinical endpoints out here are not enough to really support this

at

model.

I should also mention that the claim that we really make here is that we noted at weeks 32 and 40, the combination therapy group really shouldn't included in the statistical significance of the prognostic value of the change from baseline because there weren't enough ADEs in that to combination therapy ddC plus saquinavir.

So, really, for only weeks 32 and 40 can we say that the prognostic value, statistically at least, is supported in the two monotherapy groups.

[Slide.]

So, to summarize the statistical case, for study weeks 4, 8, 16 and 24, in the combined-groups model, we see that the risk of the first ADE decreased in all three groups with a decrease in the last RNA. This was after adjusting for all of the other variables.

We are able to see, in weeks 32 and 40, a similar result except we can only state that for the monotherapy groups. Finally, we don't see a statistically significant decrease in the risk beyond week 40. As I said before, we think that is probably due to the lack of events for this particular model.

What I would like to do next is attempt to characterize what the clinical significance of this is and

at

really focus in, perhaps, on the actual effect size that was estimated.

[Slide.]

Let's focus on week 16, for example. Here we have the four--this was just one of those boxes that you saw from the previous slides. We are focussing on this particular coefficient, the change from baseline, statistically significant. What does this mean for this particular study?

It was the case that, after you eliminated the few patients that dropped out because they had their first ADE prior to week 16, that, for baseline RNA and baseline CD4, all three groups were about the same in baseline RNA and baseline CD4 at week 16.

So that means that any differences that were present in those three groups in terms of their subsequent risk of progression perhaps would be associated with baseline RNA and baseline CD4.

Let's see what that is.

[Slide.]

It turns out that, for the saquinavir group, there was really just a tiny--and tenth of a log--treatment-induced reduction in the RNA by week 16, from baseline. There was a somewhat larger reduction, about 0.4 logs for the ddC group and even a somewhat larger,

at

approximately 0.6, reduction in the combination therapy group.

If you put those reductions into that Cox model and focus on the change from baseline term, just due to the change from baseline term, what is the reduction in risk of progression when compared to patients who had no change from baseline.

This particular column gives the answer, that you really multiply the risk by 0.92 for this small reduction therefore resulting in about an 8 percent reduction. So this small decline in RNA yields about an 8 percent reduction. This medium-sized decline yields about a 20Êpercent reduction.

Finally, in the combination-therapy group, the group that performed the best, this half-log reduction yielded about a 30 percent reduction in risk. That is the value that we are talking about, I guess. Relating the statistical model to estimates of reduction, we can see differences here and we, then, can say that there is evidence from this modeling that this could be a very useful exercise and certainly suggestive of being able to monitor anticipated risk reductions as a function of the change from baseline.

[Slide.]

at

What I would like to do very briefly is go through and just, in a very descriptive way, give you an idea of the range of all of the covariates, the ranges from low to high of all of the covariates, and give you an idea of the range of risk that was encountered in this study.

What we did first was we eliminated a very low risk group so that we didn't artificially inflate the risk factors. We basically used the early groups. I am going to focus on study week 16 here for this descriptive analysis. All we did, really, was that for each of the patients, we put all of the patients together into one big group after eliminating the low baseline RNA patients, and we calculated a number for these patients.

This number came from a Cox model. It is a matter of their baseline and last RNA assessments and CD4 assessments, plugging them into a formula and coming up with a risk index for these patients.

[Slide.]

We, then, simply ranked the patients according to risk index and then simply formed several groups in the order of the risk index.

[Slide.]

Then what we did, in order to directly estimate the change in hazard or the risk of an ADE in each of those

at

risk groups, I went to a particular model which allowed me to directly calculate the hazard ratio and actually directly test the assumption of proportional hazards. The hazards were proportional in this context.

We also estimated, for each of these groups, the mean values of each of these independent variables, to kind of give you an idea of a profile and an associated risk.

[Slide.]

So what we have is this table of the seven risk groups. This first group is the reference group. Everything would be compared to this particular group. You can think of this group as sort of healthy-profile group. Basically, in terms of logs, it is kind of hard to read; it is about 60,000 copies per ml baseline.

This represents a reduction down to 10,000 copies per ml, and similar sorts of things for the CD4. Then everything is compared to that. Notice that the hazard ratios go up to two times. The next group is really a doubling of the hazard, doubling of the risk. It stays fairly low and then it begins to increase dramatically and can get into the worst profile, the most unhealthy profile, of a high baseline, very low change, similar kinds of things for the CD4, to up to 19.

Here we are saying it is not just the change from

at

baseline. The change from baseline, we established, is important. It does add value in addition to all these others. But all of them can be used to see the effect of progression to ADE.

[Slide.]

Here is a plot of this change, going from the low-risk group all the way to the high-risk group to give you an idea of an approximately 1.8 log spread for the last RNA levels and the corresponding increase in the risk. This really gives you an idea of the range of risks that we are dealing with and the range of last RNA levels.

But the last RNA is really like a marker for all of these things. CD4 is varying. Baseline is varying.

[Slide.]

So, really, in conclusion, for this particular study, we were able to show an association, a strong association, I think, with progression to AIDS and the last RNA assessment. This association was demonstrated after adjusting for the other variables in the study.

We are also able to show that the amount of reduction attributed to the change from baseline is reasonable. It is useful and can be used potentially for patient management.

Thank you very much.

at

Clinical Conclusions from The Data Analysis

MR. NELSON:

[Slide.]

DR. SALGO: Now, I would like to summarize a little bit to bring this back to the clinical relevance of these findings and the focus of this meeting. As I mentioned earlier, this study was done a few years ago. We had a range of baseline RNA. They were in the range of 5Êlogs. The treatments that were available, saquinavir plus ddC, within the study allowed about a 0.6 log drop from baseline, the changes from baseline that had been the focus, or on of the focuses, of Dr. Miller's presentation.

So we have to keep in mind that the conclusions of this study are really within the framework that were possible within the study; in other words, within the range of baseline values and within the range of change from baseline values.

However, those limited declines, 0.6 logs, did afford to demonstrate the superiority of combination over monotherapy and also showed that both the baseline and the on-treatment viral load is important in assessing the subsequent risk of progression to an AIDS-defining event.

So we have to keep in mind that this is within the context of the ranges seen in the study.

at

[Slide.]

First of all, it was clearly demonstrated that baseline, of course, is very, very important. I think that this is an assumption made prior to coming to this meeting. Basically, within the context of the study--in other words, within the range of values of the study--those at the low end with less than 10,000 copies at baseline or who achieved a drop to less than 10,0000--again, the low end for this study--had the lowest progression to AIDS of patients in the study. So that is sort of the low-risk group.

Any increase in the baseline, but certainly any increase in the change from baseline or last value, had a dramatic increase in the risk of progression to an AIDS-defining event.

[Slide.]

Indeed, this increase, the more you got up, it appeared to be an exponential, led to about a 19-fold increase in the risk comparing the lower risk groups within the patient population to the higher-risk groups. A change from baseline is a little bit more than 0.5, about 0.58 or 0.6, on the combination group at week 16 and led to a 30Êpercent decline in risk to progression to an ADE.

[Slide.]

So this particular analysis within the context of

at

the study showed continued prognostic value of serial measurements on the effect of antiretroviral therapy, so on treatment effects. I think that this is important in terms of the clinical utility for patient management.

I point out that once we leave this study and come back to where we are now historically with HIV treatment, the current treatment guidelines, as Alex Wesolowski mentioned, we have the HHS guidelines and the meeting that the FDA had last July about therapy and surrogate markers.

Basically, two things have emerged; first of all, that new triple-combination therapies, especially in naive patients, or those with low viral load, are able to achieve suppression of viral load much greater than was seen in this study and, indeed, can get below the level of quantification, below 400, in a substantial proportion of patients.

So I think what we are saying here is the treatment effect--in other words, the change from baseline--is much greater than was seen in this study and, therefore, would be expected to be a more important variable in the serial measurement of prognosis for that patient.

Indeed, such profound viral suppression would be expected to result in even further decreases in risk of progression to an ADE.

at

[Slide.]

Thus, we feel that these data support the claim, the proposed claim, for the Amplicor HIV monitoring test which is to monitor the effects of antiretroviral therapy and for the management of HIV-infected patients by these tests. I think, clearly, this study showed the prognostic value of serial measurements for monitoring patients.

I think after the break we will hear a further description of another study, the CCTG570 study, that was a part of the phase IV commitments of RMS. The reason that that is not included in the package is simply because an interim analysis is just recently available and that is what will be presented. However, it is part of an ongoing commitment.

Thank you very much.

DR. HOLLINGER: Dr. Dayton?

DR. DAYTON: I wanted to ask a couple of questions. This wasn't a setup. This is just a straightforward question but I need some of your slides. Let me see if I can go back to them. I need to go back to the statistician's slides.

[Slide.]

In this particular slide, if I remember right, you are saying that for a 0.13 log decrease in the RNA

at

ratio--was that last to baseline?

DR. MILLER: Yes.

DR. DAYTON: You are getting an 8 percent drop in the hazards; right. Okay? And then, for a 0.3 log, or almost 0.4 log, it is a 20 percent drop and then a 30Êpercent drop when you go up to 0.5 log. What I would like you, as a statistician, to point out because I don't understand--in doing this, you have compared saquinavir to ddC, to saquinavir plus ddC, basically three different arms of the study; right?

DR. MILLER: Right.

DR. DAYTON: But I understand that you get different hazard ratios with different studies; right? They are not totally proportional. You get different hazard ratios for saquinavir and ddC. The three different arms have three different hazard ratios, don't they? So are you comparing apples with oranges?

DR. MILLER: All I really did here with a combined-groups model, I took that coefficient of the Cox model and simply--the combined-groups model meaning all three groups combined together. I took the corresponding coefficient which was, I think, 0.6 for the change from baseline which was estimated the same for all three groups.

But then I multiplied it by just the realized mean

at

reduction, more as an illustration than anything else, showing a low reduction versus a higher reduction. And that is all I did.

DR. DAYTON: Let me ask, in this case, here, we have two levels which are below the variability range and one at the minimum variability range. Is this data here something on which you would base a claim saying we could take a subset of patients and make a prediction that is useful to them, or is this just illustrative data.

DR. MILLER: This was illustrative of how one might use this result. Here I was simply trying to relate the abstract Cox model coefficient to something that would be somewhat more meaningful.

But those changes were changes in the mean, changes in the average. I wasn't speaking to an individual patient there.

DR. DAYTON: Okay; so this would be illustrative data. Let me go on to another side of it on which I had another question. You may want to stay up there. It is hard dealing with somebody else's slide.

[Slide.]

I believe this is just a tabular form of this; right?

DR. MILLER: That's right.

at

DR. DAYTON: That is risk ratio on the bottom?

DR. MILLER: No; that is the last RNA.

DR. DAYTON: Okay; that is actually an RNA.

DR. MILLER: That's right.

DR. DAYTON: I can't read those numbers. What are those?

DR. MILLER: That is 10,000 copies there.

DR. DAYTON: This is partial logs?

DR. MILLER: No; that should be, like, 4.0 as the low point there. It is about 4.0. Then it goes up to 5.something.

DR. DAYTON: Here.

DR. MILLER: Yes.

[Slide.]

DR. DAYTON: And then this is 6.0.

DR. MILLER: Yes; approximately.

DR. DAYTON: So it is really only a 2-log range.

DR. MILLER: 1.8-log range.

DR. DAYTON: That has not been clear to me, but that is good. Then this was the overall risk hazard index, right here?

DR. MILLER: That's right. That is the hazard ratio.

DR. DAYTON: And that 19-fold change takes into

at

account everything, CD4, baseline, last and everything.

DR. MILLER: Yes; it does.

DR. DAYTON: What was the part of this that is just due to sequential RNA measurements, because that is the number that is central to the claim here?

DR. MILLER: I don't know that I actually estimated that. I think I would just say that the baseline RNA was probably the most important and then second was the change from baseline, if I had to rank that. I didn't actually separate those hazard ratios out in that particular slide.

DR. DAYTON: What is absolutely central to the claim here, for a management claim, is how much of this ratio is due to sequential RNA measurements of some sort. For instance, if this change of 19-fold, if 18 of it is due to baseline plus CD4--this would include CD4 and changes in CD4; right?

DR. MILLER: Yes.

DR. DAYTON: If 18 of it or 19 of it is due to those numbers, what that means is, and maybe it is significant, but the small change that is due specifically to the sequential RNA measurements is statistically significant but clinically irrelevant.

So can you give us a hard number on exactly what

at

the contribution would be? That would come out of one of your relative hazard ratios, wouldn't it, at some point?

DR. MILLER: It actually comes out of a previous slide. Here we go. That was not the intention of that particular slide to actually--the intention of that slide was to really give the range for all covariates. Let me go back

[Slide.]

This is the unique contribution to the change from baseline from the Cox model. It is statistically significant and the size of this coefficient and the direction of the coefficient--it is not as large as the baseline RNA, certainly. Size is not necessarily a good indicator. You have to multiply by something in order to get a sense.

But we are not talking about, really, a trivial effect here. But this is the slide that establishes that there is a unique contribution to the change from baseline after having taken these into account.

[Slide.]

This, then, relates that to being able to discern or say 8 percent risk for a low change to 30 percent reduction for a reasonably high change. That is coming directly from the unique contribution to--

at

DR. DAYTON: Just so I can get more of a feel for this. I appreciate your answer because it really is focussing on the central question. Translate this 0.6 number to me for what that says to the physician. Okay; you see a ten-fold drop in your RNA and now you tell the patient--

DR. MILLER: You see a ten-fold drop. That is one log. You multiply that by 1, and then you take the negative exponential of that and that is the hazard ratio, predicted hazard ratio, compared to patients who didn't drop at all.

DR. DAYTON: And the answer is?

DR. MILLER: What is e to the -0.6?

DR. DAYTON: Okay; if it hard to calculate.

DR. MILLER: No; it is e to the -0.6.

DR. DAYTON: Paul, will you point that out in your talk, because we don't need to do that now. I think that is really a central question to the claim which is why I focussed on it.

DR. MILLER: I think it is basically here, is that separation.

DR. SALGO: If I could just address that from a clinical perspective and not try to quantitate the coefficient which, honestly, I don't understand. But in terms of the change from baseline that was seen--in other

at

words, focussing only on the treatment-induced change from baseline, the best arm for this study showed a 0.6 log drop from baseline, change from baseline.

That was associated with a 50 percent decline in progression to AIDS-defining event compared to the control arms that had much smaller change from baseline, so a difference between those two arms of about 0.5. Actually, that is quite similar to the effect that we see here which is looking at the 0.6 log drop affords a 30 percent decline in this particular analysis which is not comparing the arms but only within the arm.

So I think that the way I see the clinical importance of this, even though the changes from baseline that were seen during the study were relatively small by today's standards, they had a profound impact on the clinical progression to AIDS.

DR. HOLLINGER: Could I ask a question. I don't want to get into the issues right now, but I just need some information about the testing. These were done on EDTA, ACD, heparin serums? What kind of plasmas were they--not serum; but what kind of plasmas were they? That is the first question.

DR. SALGO: As I recall, they were EDTA. This was all done prospectively. It as planned using the Roche

at

system of prototype by Labcor and I believe the validation has been done.

Does anyone want to speak more on that?

DR. HOLLINGER: But it was EDTA plasma?

DR. SALGO: I think it was EDTA.

DR. HOLLINGER: How many laboratories performed the assay during these times?

DR. SALGO: This was one centralized laboratory.

DR. HOLLINGER: So it had a centralized laboratory. Was it done in batch?

DR. SALGO: Yes; it was done in batch. This study was done prospectively primarily to get saquinavir approved, so we did not know, at that time, the variability of these assays, et cetera. I think, subsequent to that, it has become clear that some of those issues--for example, batching--are a little less important than we had anticipated.

For, for this particular study, it was centralized lab and it was batched.

DR. HOLLINGER: That is important because many samples are done real time in the real world. We need to understand that because it makes a difference in looking at data.

The other issue is with the Amplicor, in a single

at

laboratory, what is ability, at a 90 percent power, to detect a five-fold difference in the assay. This is critical because most of these assays--I think it is important to point out--most PCR assays can probably only detect a five-fold difference, maybe a three-fold in some circumstances by doing batch testing, one laboratory, and so on.

But I think you are really stretching it and what is really pushed is to detect a five-fold difference at a 90 percent power. If that is the case, and these are starting at 100,000, that means that they could probably detect the difference between 20,000 and 100,000, over time, but may not be able to significantly detect a difference of 100,000 down to 60,000 or something of that nature.

That is important here in the issues here when you look at these log changes, I think. So maybe someone from Roche might be able to also tell us what is that ability to detect the difference.

DR. SALGO: If I could, perhaps, address some clinical aspects and then, perhaps, Dr. John Sninsky could address some of the issues about the variability of the assay.

First of all, we have to keep in mind that, in this particular study, we are looking at group data. So the

at

0.6 log drop is not a 0.6 log drop in one individual. It is an average of many, many patients. So, obviously, that has a certain confidence interval.

Now, I think, as was clearly demonstrated in last July's FDA advisory meeting on surrogate markers, the variability of the assay includes the variability of the assessment and, also, patient variability. But, generally, a change of greater than half a log is considered to be a real change in an individual basis.

So here we see a drop of 0.6 log, et cetera, that is on a group basis so we have much more power there.

John, would you like to add to that from the perspective of the assay?

DR. SNINSKY: The question is a good one. We have to distinguish between the data that was accumulated in the submitted application and then the data that is out in the field. Obviously, the data out in the field is, for those of you who attended the July FDA meeting, much, much greater than the data that is in the application, itself.

Let me use as an example, in Marchner's summary in the Hamburg meeting recently where he looked across eight clinical trials in the ACTG and looked at multiple assays, pertinent to this meeting are the Roche Amplicor results. He concluded that, for clinical benefit, it required a

at

change of approximately 0.5 logs of viral logs for this assay.

So I think that the experience in the real world is that the standard deviations are such that 0.5 log changes could be discerned. So I think it is important to both look at this data which is 0.589, approximately 0.6, relative to real field experience.

Does that answer your question, Blaine?

DR. HOLLINGER: Yes. Thank you.

DR. MATHEWS: To try and understand what is going on after week 40 where the prognostic value of sequential measurements is less apparent, could you tell us what percentage of the patients in those latter risk sets were on blinded therapy at the latter parts of the study?

DR. SALGO: As you recall, the median duration of therapy was approximately a year. So we are coming to the end of that time period. However, the duration of follow up, the median was about a year and a half. So patients were followed.

I think, basically, as I understand and Dr. Miller can give some more specific answers, that the major reason--the hypothesis of why we are losing power at those subsequent weeks is simply because of the whole cohort of patients, fewer and fewer events happened at that tail end

at

of the period. That is the length of time we followed people and that was the duration of the study.

So, as fewer and fewer events, especially in the most effective treatment group, of course you lose power.

DR. MATHEWS: I think most of the analyses that you presented were stratified by original treatment assignment, intention-to-treat. If treatments were changing, particularly as people went off blinded therapy, you would have some confounding with the marker changes with treatment changes also.

DR. SALGO: Basically, most of the time that they were getting their RNA measures, they were on treatment except if they had had an interruption or something like that. The clinical follow-up period, it is true that they could have been on other treatments. However, at that time, 1994, 1995, there were limited other options available.

So we think that that had a limited impact and, thus, we were able to see the clinical differences even though they may have been on different therapy subsequent to that.

Mike, do you want to add anything about the last--

DR. MILLER: No.

DR. BOYLE: Quick question. The regressions that you generated will have a classification function, can have

at

a classification function. One of the things that would be very helpful to us to know is what proportion of cases is correctly classified with the baseline information only and what is the improvement in the classification by the addition of the change scores.

Can you tell us anything about that?

DR. MILLER: I know what you are referring to. I did not do that analysis so I wouldn't have that information for you now. I think that analysis would probably end up to give a favorable result given the strength of the results that we had in the regression. But I don't have that for you.

DR. HOLLINGER: I am going to ask the FDA to give the summary and critique and then we will come back to any questions here unless someone has some questions they would like to ask specifically right now about the data that was presented.

This will be by Dr. Paul Flyer.

FDA Summary and Critique

[Slide.]

DR. FLYER: I am Paul Flyer. I am from CDER. The reason that I will presenting the FDA statistical analysis is because of my previous involvement with this trial. I had reviewed the saquinavir application for traditional

at

approval a little over a year ago and I have received some statistical support from CBER from Drs. Lachenbruch and Wang.

[Slide.]

I will quickly go through the review of the study design and the outcomes. We have seen a lot of that already. I will try to highlight the company analyses that I found most interesting and persuasive and talk a little bit about the analyses that I found a little bit of less interest.

I will also present some additional analyses which I think will clarify some of the questions that we just were going over. I think it is important to keep stressing that these data are historically a little bit different than what we would be seeing today, but I still think we can make valid assessments of the utility of using the assay based on these data.

I will get into some of the implications of this particular data in terms of the conclusions that we are debating at the moment as I go on.

[Slide.]

So, as discussed, this is a randomized, double-blind trial with ZVD-experienced subjects, CD450 to 300. We had seen the data once previously for accelerated

at

approval where we looked at primarily short-term CD4 changes. At the time, we were placing less emphasis on HIV RNA. Then the data came in once again for traditional approval based upon AIDS progression.

I think, as has mentioned before, we are concentrating on overall patterns in the data, consistency rather than test the significance since these are all post-hoc analyses that are quite exploratory in nature. But I still think that we can glean the associations from these data.

[Slide.]

Just to reiterate the patient assignments. There was, actually, a fourth arm in this trial but it was discontinued early due to lack of efficacy. There were roughly 100 patients randomized to that arm, relatively short duration of follow up, so it has been excluded from these analyses.

I am comfortable with that approach. We can also see that roughly a quarter of subjects experienced a clinical event on trial with noticeably fewer in the combination saquinavir/ddC arm. But you also can note that one-sixth of the patients were not followed until either administrative closure of the study or until an event had occurred.

at

I have some analyses with that. They tend to have somewhat worse CD4 response, the subjects that dropped out. HIV RNA did not change too much from baseline for these subjects, but I didn't notice any differences among the treatment arms with respect to characteristics of the subjects dropping out.

Since there is also rough balance in terms of the numbers across the arms--so we are losing some of the subjects who, perhaps, didn't respond as well to treatment, but it doesn't appear that it is so dramatic that it would affect the conclusions we can reach from the study.

[Slide.]

We have seen this before. This is Kaplan-Meier curve for the time-to-clinical-event. The yellowish arm is the combination therapy and the two monotherapies are below. They look quite comparable. You can also see that the overall risk reduction is fairly substantial but the risk, itself, is not that high.

So out approaching a year, it is roughly 10, 15Êpercent of the subjects have had an event. So we are seeing relatively large relative drops on a relatively low underlying risk.

[Slide.]

So the company has presented analyses in the first

at

part of their presentation on the treatment effect explained. Then we got into the Cox models, the assessment of response to therapies, what it is sort of called in the submission. Lastly, they talked about a risk score. I will be focussing primarily on the assessment of response to therapy.

I have not been a big fan of the treatment effect explained, especially for this particular application. We don't have a real good handle on sort of what proportion the variance explained leads to an acceptable surrogate. It probably depends a lot on the particular application.

We would accept a lower percentage in a very severe disease like this whereas a higher proportion explained, or even perfect dissociation, would be required in other situations. Also I think as the applicant has shown, even in a situation where there is no real treatment effect--essentially the saquinavir monotherapy--you can still have a good predictive value from the assay results, so I think that those analyses on surrogacy are interesting but they are not really key to what we are doing today.

Similarly, the risk score is based upon models, the more complicated models of pooled analyses over arms. I will be discussing some of the limitations of those models. It is important to keep in mind the adage that all models

at

are wrong but some are useful.

I think, for this particular situation, the risk score is based upon models that, perhaps, are not completely appropriate and it is really just a repackaging of the analyses that I am calling the assessment of response to therapy. So I don't think it is giving new information. It is just trying to provide some additional descriptive information.

But I have some slightly different ways of presenting the results of the trial which maybe will help. Finally, the risk scores we have discussed sort of obscures what is going on with just the change in HIV RNA because it is an amalgamation of both baseline measurements and the change in CD4 and HIV RNA.

So I will only be emphasizing the assessment of response to therapy as we discussed earlier. We looked at baseline HIV RNA, CD4 at baseline and then the relative changes and that this was done at weeks 4, 8, 16, 24 et cetera.

[Slide.]

As the applicant mentioned, there are some issues with proportionality. I agree with their assessment that, in fact, I don't think they really interfered dramatically with our interpretation of the results. But there are

at

enough departures from proportionality that I think the models are somewhat suspect.

I think they are quite useful and interesting for summarizing the data, but I think as we get into it, you will see that, in fact, maybe we don't want to rely on the models for making precise predictions but they are useful, I think, in summarizing some of the aggregate patterns that we are seeing.

In particular, I think it is the differences that they noticed in the response by treatment arm.

[Slide.]

So I will talk about some of the statistical methods and the problems, what the Cox models are showing, try to get into the internal consistency of the results and then we can talk a little bit later about what would one need in order to generalize the study results in a very precise way as opposed to just finding associations in this particular study.

[Slide.]

This is an exerpt from the submission from the applicant. This is the Cox model. So what we are seeing here is that for those subjects who made it to 16Êweeks or to 24 weeks, in the model that only includes baseline HIV RNA and the change in HIV RNA, when you fit separately for

at

each treatment arm.

The other models that were produced by the applicant said essentially that the model-linking change in HIV RNA at baseline, the coefficients are the same across the three arms. That is an assumption which I think that this particular table, and that the applicant has indicated before, may not be completely true.

So this is also another way of summarizing. For example, the 3 suggests that there is a reduction in risk at about a factor of 3 in a 1-log change from baseline for saquinavir monotherapy but that it is actually only 1.7 for the combination therapy.

So it raises the concern that if you need to know a person's particular treatment in order to know what is their risk reduction associated with a 1-log change, this is somewhat problematic. But I think as we go on, it is more of an issue with the particular models they fit rather than with the assay itself.

We will see that the changes that are going into the model are fairly different for each treatment arm; more pronounced effects in arm versus less in another. One aspect of the nonproportionality is that changes, for example, going from 1 to 2 logs are not necessarily the same

at

as going from 0 to 1.

So if you fit models based upon sort of an aggregate of data for each arm but they are covering a different range of changes, you could, perhaps, expect to see different model parameters even though the assay is still behaving in a good fashion.

With these models, you want to simplify things. You say it is a simple linear relationship, that 1-log changes are the same regardless of where they occur. It is difficult to expect that that would be the case, but, from a modeling standpoint, it is very useful for summarizing the data.

I think we will see this in a later slide.

[Slide.]

What I will do now is go through some of the analyses that we conducted to further illustrate what are the ranges of changes in the data, what are the implications on the models they fit. So we will look at first the distribution of changes from baseline.

This will actually bear upon the variability in the assay as well. We can see where that half a log variability is coming from. We will look at the proportion of subjects below 400 which where, I think, we are looking now for effective therapies to be--see if these data really

at

have much to tell us about that, look at the subjects who have had a half-a-log reduction that is maintained over the course of the trial which is beyond the limits of variability of the assay.

Then we will look at the relationship between the clinical events and the baseline HIV RNA and the change. I will try to plot it simultaneously so that we can see how these things are working in a joint sense.

[Slide.]

This is the distribution of the changes by treatment arm. You can see for the saquinavir monotherapy, which is the white line, most of the values are in the range of negative 1-log change to positive 1-log.

There is a slight shifting with ddC monotherapy to the left. It is no longer centered at zero and, with the combination therapy, it is centered a little bit more to the left. These are the changes at week 16. I have focussed on that.

For historical reasons, we tend to look at the short-term changes and see, well, what do they tell us about the clinical events later on. This is somewhat how we would want to see patients, perhaps, evaluated with respect to their treatment.

You start treatment. A couple of months later,

at

you check to see how they are doing. So is this going to be predictive. I think the rest of the results are consistent with this, but I tend to find this to be most useful.

Out here, we had a number of changes that were actually missing. On the order of 15 to 20 percent of the week 16 values weren't present. So, if we look at saquinavir monotherapy at 16 weeks, the changes are on the order of the negative-1 to 1 log. What I have also done is gone out further into the data, about a year, and looked at the visit-to-visit change for the same subject.

At that point, I think with these treatments, we are in a very stable situation. There, the standard deviation was a quarter of a log. So if it is any change of over half a log, it is outside of two standard deviations. So those, I think we could conclude, are real changes.

Smaller changes could also be real but anything over a half, we can be very comfortable, is a real change in the underlying HIV RNA for an individual subject.

[Slide.]

So, as I think as mentioned, for historical reasons, these particular therapies achieved very low proportions of subjects below 400 which suggests that the utility of the study for telling us about what is the clinical outcome of subjects with very pronounced

at

suppression, this study cannot really provide us information on that.

[Slide.]

Lesser changes, in terms of a half a log, sustained reduction. So the first time a patient comes back up over the half-a-log change from baseline or they are within a half a log, starts at about 50 percent for combination and relatively quickly goes down to a fairly low proportion of patients over time are having a sustained half-a-log change.

This suggests that the analyses, as you go out further using progressive subsets, you are almost back into the situation where you are not having treatment-driven HIV RNA, you are almost back into a natural-history mode. Once you get past 28 weeks, 36 weeks, very few patients are still benefitting from their initial therapy.

[Slide.]

It is just something to keep in mind as we consider the applicant's analyses. This drives home what we already know, that baseline is important. If you start out at 100,000 copies, you have a fairly low risk of developing a clinical event; 10 percent on saquinavir monotherapy, 5Êpercent on combination therapy.

You are seeing much more pronounced risks of

at

progression for subjects who start at over a half a log. So now what we want to know is if you throw on top of this a measurement made after this initial baseline measurement, does that give us additional prognostic value.

[Slide.]

This is a little unfortunate the red is not showing up that well. But what we are showing here is I have broken out the subjects by their baseline value. The red line are those subjects who started out over 100,000. The white line are those that started out at less than 100,000.

There is a red dot there that suggests that there is a fairly high probability of having an event if your baseline was missing and you started out at 100,000, that those are subjects who tended to have a worse prognosis.

If you start at less than 100,000, and your 16 weeks was missing, things aren't too bad. I am just doing this so that all the subjects are represented in the data. A lot of a applicant's analyses excluded various patients who were missing so we didn't know what happened to their clinical outcome.

They have also excluded subjects who are less than 25,000. I have tried to use all the subjects who were randomized to these three arms. So the pattern shows that

at

for--this is your actual value, not the change, at 16 weeks. This says that, at 16 weeks, if your value is higher, so less than 10,000 would be the best prognosis, going up to over 200,000. That is the worst place to be, 16 weeks independent of baseline.

The actual baseline isn't too predictive for most subjects. You want to know where you are at 16 weeks, which gives you most of the prognostic value according to this graph, except for this one group. 50,000 to 100,000 at 16Êweeks, it is worse if you started at 100,000 versus starting at less than 100,000.

I have interpreted this to mean that you are catching people on the way back up again at 16 weeks. If, at 16 weeks, you started at less than 100,000, you are probably not going to get that much worse as therapy wears off. But in the group that was 50 to 100,000 at 16 weeks, but started over 100,000, it is very bad to be going up in terms of your HIV RNA copy number at 16 weeks, that these patients are probably headed back to baseline which is not very good in terms of their prognosis.

We had very little data on subjects who started out at less than 100,000 who were, then, over 200,000 at 16Êweeks. So I chose not to even put their data up there because it is only eight subjects.

at

[Slide.]

This is another way of breaking out the applicant's analyses. The dashed lines are subjects who started out at over 100,000. The solid lines are those who started out at less than 100,000. I have broken it down based upon their change at 16 weeks from baseline; less than half a log, half a lot to three-quarters of a log and over three-quarters of a log.

Then I looked at their prognosis over time, what is their clinical outcome. So this is a standard Kaplan-Meier curve just broken out into six subgroups. The group that has the worst outcome is blue line. They start at over 100,000 and they had essentially no treatment effect at 16Êweeks.

Their HIV RNA is within a half a log. They are much worse than everyone else. The other two dashed lines represent subjects who also started over 100,000 but this group had a half-a-log to three-quarters-of-log drop at 16Êweeks. Then the red dashed line is those who had greater than a three-quarters-of-a-log drop.

So we see a progression; start out at over 100,000 which is where most of the events occurred. The bigger your drop, the better your outcome. The three solid lines are in the same sort of order. It is better to have a higher drop.

at

But there is a fairly low risk associated with having an outcome so that we don't see that much separation.

So this is the particular graph that I have been using which best describes what is going on in terms of the underlying risks and the risk reductions associated with the various changes in HIV RNA.

You also note here that I am only going up to three-quarters of a log. It is difficult to use these data to suggest what might be happening to subjects with a bigger drop. I think it will be consistent with this but these data don't really tell us sort of how is the relationship going to change.

Can you say that sort of going from three-quarters of a log to one-and-three-quarters to two-and-three-quarters that you will see the same sort of progression? We don't know. You could have a compression. You could have exponential growth.

These data don't tell us. But what they do tell us is that there is a pretty strong association between the changes seen at 16 weeks and where you are eventually going to end up and that it does contribute over knowing just their baseline value.

[Slide.]

That is essentially my summary, that we have seen

at

that the changes in HIV RNA copies are associated with eventual clinical outcome. We still have some questions remaining regarding the precise relationship and, as was cited earlier, there is a lot more work that needs to be done.

I think we are just beginning to learn how to use these assays to predict what is going to be happening to particular patients.

Thank you. Any questions before I step down?

DR. HOLLINGER: Thank you. We have some time. The reason I was trying to find out what we could or could not do is because we have an agenda and some people come specifically for things that are presented at a specific time.

I think what we are going to do is we are going to go ahead and take our break now. It is now 9:50. We will break until 10:15 and then we will start with the open public hearing at that time.

[Break.]

Open Public Hearing

DR. SMALLWOOD: For the open public hearing session, I have been notified of three individuals that will be speaking during this time. If there is anyone that would

at

like to speak during the open public hearing and has not contacted me, would you please let me know before we begin at this point.

If not, then we will proceed with those individuals that I have knowledge of. I would ask that everyone try, as close as possible, to remain within the time frame that has been allotted to you so that we may continue with our agenda as printed.

Thank you very much.

DR. HOLLINGER: Thank you, Dr. Smallwood.

The first speaker in the open session is Dr. Richard Haubrich from the University of California, San Diego.

DR. HAUBRICH: I would like to thank the committee for the opportunity to present this data here today which I hope will be interesting and, hopefully, relevant to the topic under discussion.

[Slide.]

HIV RNA is now the standard of care for managing, initiating therapy and manipulating that therapy for patients treated in the clinics. It has been well shown that a single HIV RNA measurement is an independent prognostic factor of the time to clinical disease progression and death.

at

In addition, as presented earlier this morning and in several published studies, treatment-induced reductions in HIV RNA are well correlated with reduction in clinical progression.

I illustrate with one introductory slide here some data published in the Annals of Internal Medicine just a couple of months ago showing that patients treated with nucleoside therapies, if they had a reduction in RNA of at least 0.39 logs, they were less likely to have clinical disease progression across the spectrum of baseline RNA compared to patients that failed to have reduction in RNA suggesting that treatment-induced reductions have clinical relevance.

[Slide.]

However, none of the studies to date have used HIV RNA monitoring in a clinical setting to initiate and manipulate antiretroviral therapy. It was with that idea in mind that Allen McCutchan and the California collaborative treatment group initiated CCTG570.

[Slide.]

The results I am going to present to you are the results of an interim analysis that was preplanned after approximately 1,200 patient months of follow up. The necessity for an interim analysis in this study was brought

at

about by the extreme pressure in the clinical setting to use HIV RNAs in all patients.

[Slide.]

Our hypothesis for the study was as follows. We felt that high levels of HIV RNA are bad and that the goal of antiretroviral therapy is to maximally reduce RNA for as long as possible. We felt that, by monitoring HIV RNA, we should be able to improve the antiretrovirals that are selected and switched by the primary providers.

This should result in better suppression of RNA and that better suppression eventually would translate into clinical outcome. The California collaborative treatment group, which is a collection of four centers with two additional centers for this study, did not have the resources to perform a clinical-endpoint study so we used an interim endpoint of RNA suppression for the study.

[Slide.]

The primary objectives of our study, then, were to examine the utility of monitoring plasma HIV RNA, in this case using the Roche Amplicor test, as a means of adjusting antiretroviral therapy with the goal of maximal suppression of HIV RNA and viral load.

We, in addition, wanted to show that suppression of viral load would translate into a better CD4 cell

at

response.

[Slide.]

This slide, which I apologize is difficult to see, is the overall study design. Patients at baseline were randomized in a prospective fashion to two clinical strategies of treatment monitoring. At baseline, we stratified by CD4, less than or greater than 50, and less than or greater than 12 months of prior therapy.

Patients, then, were randomly assigned to monitoring using intensive HIV RNA monitoring where RNA and CD4 were measured and fed back every two months as well as interim time points and predominantly CD4 monitoring where HIV RNA and CD4 were measured every two months.

But the CD4s were fed back. The RNAs were fed back only at baseline and twice during the 12-month follow-up period. Based on this monitoring, antiretroviral therapy was initiated and patients were monitored during therapy with CD4 and RNA.

If there was evidence of deterioration based on these markers or clinical changes, then a treatment switch was initiated. We spent a lot of attention to capturing the rational for treatment switches during this study although that data has not yet been analyzed since this was an interim analysis.

at

If a switch was made, then the patient was rapidly reevaluated by repeats of CD4 and RNA in this group and predominantly CD4 in this group, and the new treatment was indicated again if an appropriate reduction in RNA was not achieved.

We did not have strict requirements for which drugs should be used in this trial. Any antiretroviral that was available through an IND or for approved process was used in this study by the patients and the providers. We had no limitations on what drug or what combinations could be used.

We did, at the start of the study, make recommendations on what was the significant change in HIV RNA and CD4 based on data that was available at the time. To summarize briefly, we felt that a 0.5-log change in HIV RNA should be more than would be expected from day-to-day variation and test variation.

And so if that change was seen, that would be a meaningful change to help guide the physician in therapy.

[Slide.]

The entry criteria are shown here. We had patients with less than 500 T-cells with a good prognosis expected to live at least 12 months. Importantly, patients had to have antiretroviral switch options to enter into this

at

study because if they had no possible switches, obviously monitoring would not help you.

Patients had to have measurable RNA of at least 5,000 copies on entry to this study.

[Slide.]

The clinical evaluations are as shown here. The patients were seen at least every two months or more often if deemed necessary by their providers. At visits, we carefully captured the antiretroviral regimen the patient was on. What we call the baseline regimen is the regimen the patient is on at the time of starting the study.

Since all patients in the study had positive HIV RNAs at baseline, it would be presumed that they would undergo a treatment switch close to the time of initiating this study.

In addition, we carefully captured the rational for antiretroviral changes and AIDS-defining clinical events although we did not have power to show differences in those. As I mentioned, HIV RNA was measured in real time in both groups, but fed back only twice yearly and at baseline in the CD4-monitored group.

[Slide.]

The primary endpoint for this study is the area about the change from baseline in HIV RNA and CD4. We felt

at

that an integrated area would be more informative than a simple change from baseline since it would accommodate and account for all of the RNA values that were available during the study.

[Slide.]

The area about the change from baseline is simply calculated by plotting the change from baseline and calculating the area using simple geometry. Even a non-statistician could do it.

[Slide.]

These are the considerations at the beginning of the trial for our sample size which was 200 patients. In addition to the 200 patients, we randomized the study 1.5:1 to RNA-monitored versus CD4-monitored groups in an attempt to encourage patients to enroll in the study.

The data here is from an early ACTG study in which they had approximately a 0.4-log decrease in RNA with time giving them 2.4 copy months of RNA over a six-month period. We postulated that if our two groups, the RNA-monitored and the CD4-monitored group, had a difference at each time point of 0.25 logs, shown in this band down here, then the area difference would be enough to be able to detect a statistical significance at the 0.05 level with 80 percent power.

at

If, in fact, there was a bigger difference between the two groups, as shown by this bar down here representing a 0.5-log difference at all time points, we would have more power to detect a difference in the study or we would be able to account for a higher standard deviation of our measurement.

[Slide.]

Since the HIV RNA with time curve can be very different for patients and may be very different depending on when you look at them, we had to carefully consider which patients to include in the analysis. This example here of a patient who had an initial reduction in HIV RNA that was lost eventually typifies what happens in patients that are not completely suppressed with RNA and they have a reduction that eventually fails.

So if you looked at this patient and included data--let's say this patient was censored at this time point because he had only had two months on study--you might get a very different answer than if this patient had been followed for the full six months.

In order to maximize the number of patients included in the interim analysis and minimize this effect of the different-shaped curve of HIV RNA with time, we included people in the interim analysis if they had at least four

at

months of follow up and censored the values at eight months.

So our analytic subpopulation is slightly less than the total population in the study.

[Slide.]

We did both a weighted and unweighted analysis which was a T-test. Fortunately, there are no Cox models to digest here. The weighting factors account for the follow-up time and for the number of RNA or CD4 values in the calculation of the area.

[Slide.]

This shows enrollment into the study. We started accruing patients in May of '96. We had hoped to enroll in six months. However, the popularity and availability of HIV RNA made the study a little bit difficult to accrue to and we finally finished our enrollment of 204 patients in July of '97.

[Slide.]

This now shows you the baseline characteristics for patients in this trial, referred to as the CD4 and RNA groups. The groups were well matched in gender, age and by randomized strata with less than or greater than 50 cells and less than or greater than 12 months of prior therapy.

The groups were also matched in terms of race and ethnicity and in terms of the clinic to which they were

at

randomized.

[Slide.]

The baseline CD4 count for this population was approximately 140 and was balanced between the two groups. The baseline HIV RNA was 4.7 log copies and was essentially identical between the two groups.

[Slide.]

As I mentioned, the patients in the analytic subpopulation that had at least four months of follow up to be included in the analysis are the ones that are analyzed here. I won't show you the full baseline characteristics for that population but to tell you that the two groups were well-balanced as can be seen here as an example with the CD4 and RNA baseline values.

[Slide.]

This shows you now the months of prior antiretroviral therapy in our cohort. This was an extensively pre-treated population of patients. Prior antiretrovirals had been received for an average of 16 to 18 months in this population, with many of the patients having at least six months of prior 3TC therapy.

Obviously, this is important in predicting the clinical response to new regimens in a heavily pre-treated population. There were only a total of 20 patients who were

at

completely therapy-naive and although the prior months of protease inhibitors on median was zero, 20 to 30 percent of patients had had some protease experience although relatively few months.

This now breaks down the groups by their baseline regimen. This is the one prior to entry when a baseline RNA viral load was achieved. Importantly here, there was a slight imbalance in the two groups in the percentage of patients that had protease inhibitors.

As can be seen here, there were slightly more patients in the RNA group than the CD4 group that had prior protease inhibitor therapy. Since these are our best drugs, it is well know that a prior protease inhibitor will dampen your response to a new protease inhibitor. This represents, we think, a conservative bias between the samples favoring the CD4 group.

As I mentioned, most of the patients had prior 3TC and, at the time of baseline, about half the patients were on nucleoside, mostly nucleoside dual therapy.

[Slide.]

This show you now in a form that is difficult to see the 33 different baseline antiretroviral regimens that were present in our 204 patients and represents the broad range of therapies that are being used in these academic

at

medical centers.

There were 20 percent of the patients that were on therapy at the time of baseline although half of those had had prior therapy and most of the patients were AZT 3TC or D4T 3TC combination nucleosides. These regimens here represent a variety of protease inhibitors.

[Slide.]

This shows the time to premature study termination. In general, there were about seven patients, shown in the line in red here, in the CD4 group who stopped study early right at the baseline. After that, the two curves track approximately parallelly.

The difference between these by the log-rank statistic was 0.06.

[Slide.]

For this study to be able to show a difference between monitoring strategies, there has to be a change in RNA and CD4 to show a difference between the groups. What I am showing here is the change from baseline in HIV RNA with time at each study month for the entire population. Each red dot here represents an individual patient at that particular time point.

As you can see, the number of points diminish as time accrues. Importantly, there is a very broad range of

at

change from baseline in HIV RNA extending from almost a 3-log reduction to some patients that had a 1-log increase in HIV RNA representing, now, the effect of the more potent therapies that are available in 1997.

[Slide.]

This shows a similar curve from the change in baseline and CD4 cell count. Again, there is a broad range of individual patient changes in CD4 cells with an average six months of about 60 cells or so increase from baseline and an overall trend towards increase in CD4 with time.

[Slide.]

This is the representation of the primary analysis for this study. The two groups, RNA and CD4, are shown. Each individual color bar represents the area about the change from baseline for an individual patient. The numbers on top represent the mean value for the two different groups.

Overall, the CD4-monitored group had 2.63 log-10 copy months during the six-month period. That is equivalent to a reduction in RNA from baseline from approximately 4.4 logs.

In contrast, the RNA-monitored group had an overall 5.26 log-10 copy months of HIV RNA equivalent to approximately 0.88 log reduction at each time point.

at

[Slide.]

The statistical analysis of this data either using the weighting statistical method or with a simple t-test was statistically significant at less than the 0.01 level.

[Slide.]

This now shows the CD4 changes in the study. Again, each bar represents an area about the change from baseline in CD4 cell count for an individual patient from the CD4 versus the RNA-monitored group. Overall, there was a 222 CD4 cell-month increase in the CD4 group and 264 in crease in the RNA group.

[Slide.]

However, because of bigger variances in the CD4 area measurement, these changes, although in the right direction, were not statistically significant.

[Slide.]

What I plot here is an analysis showing the calculated area about the change from baseline for patients that have achieved follow-ups of at least 4, 6, 8, 10 and 12 months as shown here. The white line represents patients in the CD4 group. The black line is patients in the RNA-monitored group.

What you can see is an expected divergence of the curves of HIV RNA area about the change from baseline that

at

would be expected if a consistent difference between RNA and CD4 monitoring were seen in this study, because simply multiplying by greater lengths of time would tend to make these diverge.

Importantly, though, we see that up to month 8, there is no difference in the CD4 areas. However, at months 10 and 12, these curves begin to diverge and although the number of patients, which is approximately 40 and 20 at months 10 and 12, are low, the statistical comparison of these approaches significance with a p-value of 0.07.

[Slide.]

Shown in a more traditional fashion with, again, the red line which none of us can see, is the change from baseline for each of the two monitoring strategies. RNA is shown down here. This is the RNA-monitored group with approximately 0.8 to 0.9 reduction. The CD4 group, I can barely make out right about here with about a 0.4 reduction.

The same is seen for CD4 cell count. Up to about eight months, these lines are essentially parallel. They begin to diverge at months 10 and 12, shown here, and at month 10 even though the numbers drop, this achieves at least borderline significance with a p value of 0.02.

[Slide.]

We also examined the proportion of the patients

at

that achieved an undetectable HIV RNA as defined here by less than 400 copies by the Amplicor method at each time point for patients followed up to the given months shown here.

What you can see is, using RNA-monitoring strategy, about 40 percent of the patients achieved undetectable HIV RNA compared to about 20 percent of patients in the CD4-monitored group. As you can see, here is the number of patients at each time point. This attained a p-value of less than 0.05 up to month 8 and was not significant at the later months, possibly because of lower numbers.

[Slide.]

Perhaps equally as impressive was a calculation of the proportion of the total time that a patient spent undetectable during the trial. You can see for the CD4 group, 11 percent of the time was spent undetectable versus 21 percent for the RNA-monitored group with a highly statistically significant p-value.

[Slide.]

So, in summary, then, we have shown that patients randomized to a strategy of intensive HIV RNA monitoring had significantly greater mean suppression of viral load as assessed by area about the change from baseline in RNA than

at

those who were in a strategy predominantly monitored by CD4.

Now, remember here, these patients had at least two values of RNA in the first year as well as baseline value. The average reduction of HIV RNA, using the monitoring strategy with RNA, was almost one log, at 0.88 logs, compared to a 0.44 log reduction in the CD4 group.

[Slide.]

The proportion of patients with undetectable RNA from months 2 to 8 and the proportion of time spent below the limit of detection was statistically significant in the RNA-monitored group compared to the CD4-monitored and the differences seen in CD4 cell count approached significance at later follow ups, again suggesting that there may be a lag in CD4 responses.

[Slide.]

We would conclude that a strategy of antiretroviral therapy using intensive HIV RNA monitoring may improve the clinician's ability to select and manipulate individual regimen decisions resulting in improved viral-load suppression.

[Slide.]

Therapy-induced differences of the magnitude seen in this trial, 0.44 logs, have been correlated with improved clinical outcome in published studies, as I have shown you

at

in my introductory slide, a 0.3 log reduction in RNA was associated with a clinically meaningful difference. So we think that this also improves RNA suppression but should be correlated with clinical outcome.

Many people contributed to this work at our centers in the CCTG, particularly Dr. Allen McCutchan, my protocol co-chair and mentor, centers at USC, Santa Clara Valley, U.C. Irvine and Harbor UCLA. The study was sponsored by a consortium of sponsoring agencies and industry including Roche Molecular Systems, the University-wide AIDS Research Task Force that funds the CCTG as well as Gen-Probe and an unrestricted grant from Abbott Pharmaceuticals.

Thank you.

DR. HOLLINGER: Dr. Haubrich, while you are there, again, was this done real time?

DR. HAUBRICH: The RNA values were done at a central lab at UCSD in real time for all the patients. In other words, those in the CD4 group, the RNA was run but not fed back except for twice a year. So they were all done in real time; correct.

DR. HOLLINGER: Everything was done in real time. Okay; good.

DR. STRONCEK: Was one device used to measure the

at

RNA in all the centers? Was a single device used to measure RNA in all these patients at all the centers and was that the device that we are considering today?

DR. HAUBRICH: Correct. The RNAs were all run at one single lab at UCSD. All the samples were shipped to us. The RNAs were run at the microbiology lab at UCSD using the most recent Amplicor kit and were then sent out by our data center so that physicians and patients got their values within a two-week turnaround.

DR. HOLLINGER: Were decisions made regarding what was found regarding treatment? If a patient was negative and become positive, were there some decisions made based upon the results--

DR. HAUBRICH: Correct. The whole intent of this study was to use the RNA values in conjunction with the CD4 and clinical parameters to make decisions on antiretroviral therapy. We haven't finished the analysis, but we collected and carefully stratified 40 different reasons why a treatment decision might be made including changes in CD4, clinical changes, changes in HIV RNA.

That analysis is under way but I can tell you globally, just looking at all the reasons we collected, about two-thirds of them, the clinical listed that HIV RNA was a reason for indicating the antiretroviral switch.

at

DR. HOLLINGER: Any other questions for Dr. Haubrich? Thank you.

The second person who asked to speak today is Dr. Chernoff from Chiron Diagnostics.

MR. WESOLOWSKI: Excuse me. This is Alex Wesolowski. I just wanted to clarify one of the points that was raised about the test that was used. CCTG570 is using the current and commercially available version 1.0 assay, HIV-1 monitor test. That is the one that we have defined for you today in our presentation.

DR. HOLLINGER: Thank you.

Dr. Chernoff?

DR. CHERNOFF: Good morning. I wanted to make some very brief comments about assay performance to follow-up, actually, on some comments by Dr. Hollinger about things which might affect the quantification of viral load in patients.

My comments are directed, really, towards the effect of genetic diversity on the results of assays used to look at patient prognosis and monitoring of therapy.

[Slide.]

Just briefly, as most of you know, there is a classification of HIV into two major groups, the M group which consists of various subtypes which are defined by

at

diversity in both envelope and gag sequences, and an outlier group, group O, which is genetically very diverse and closer to divergent isolates such as HIV-2 and SIV.

These genetic subtypes or clades have worldwide geographic distribution.

[Slide.]

The subtypes have an evolving geographic distribution which is changing rapidly. As we have seen from sequencing studies done here and collected at the Los Alamos database, most of the infections in North America and Europe have been of subtype B. But other subtypes are rapidly spreading into the U.S. and Europe and mixing throughout the world.

Clinically, we don't routinely subtype patients. They require assays, either serologic assays or other assays such as gel shift, HMA or direct sequencing. This is rarely done with the exception of epidemiologic studies. In order for HIV RNA quantification to be accurate, the tests that monitor them must take into account in their probe design the genetic diversity which has been defined by these sequencing studies.

[Slide.]

This is a map of the world from a recent publication which showed, in 1990, the distribution of

at

subtypes as we see in the U.S. and in Europe, mostly B subtype and then mixtures of the other subtypes throughout the world. This is obviously very important in terms of vaccine design when one is attempting to look for the appropriate antigens to use in the context of HIV vaccine research.

Here in '96, we have the introduction of non-B subtypes and this has been documented by studies done by CDC and others and a further mixing of the subtypes. The generation of diversity is believed to be the response to both the high mutation rates in HIV as well as recombination events that occur and, therefore, we have what are called genetic mosaics where the parental strains have recombined and you have progeny which have parts of envelope or gag within the sequence as defined. So we have a mixing for reasons aside from mutation.

[Slide.]

This is a recent study which documents the introduction of non-B subtypes in the U.S. It comes from Katie Irwin and her colleagues at CDC which were presented in Vancouver and just published this month in JID. What that group saw in an epidemiologic study in the South Bronx was that non-B subtypes were detected including patients who had never traveled outside the United States.

at

It is not surprising to be non-B subtypes in African patients or Asian patients who have migrated to the U.S., but this was one of the first studies to document that residents of the U.S. who presumably had sexual contact or shared needles with people from outside the U.S. were actually infected with non-B subtypes.

[Slide.]

What does this mean? Genetic diversity needs to be accounted for in probe design. This is important for comparing studies across international interventions in terms of drug therapy trials in and outside the U.S. The prognostic value of the quantification is very tightly associated with specific HIV RNA levels as has been described by the MAC studies by Mellors and others.

The changes in RNA sequence which can occur with an individual may affect the efficiency of the amplification reactions or the detection so that there may be changes in quantification which are not related to changes in the actual RNA value but in the assay's ability to detect it.

[Slide.]

The way one approaches the issue of genetic diversity has to do with how one picks the probes that are used in the particular assay. For branch DNA, we have aligned many RNA sequences for many different subtypes, and

at

isolates, and we identify through computer programs conserved sequences.

Then we select multiple probes. In many of the assays, we have developed--this sometimes can range from 20 to 50 different probes which overlap regions within the conserved areas. In the case of the HIV test, we have used the pole region. You make multiple probe sequences at each site to accommodate this sequence variation.

[Slide.]

One can formally validate the quantification of the various subtypes by making RNA transcripts in the laboratory, chemically quantifying them, and then looking at how the test behaves or performs with these RNA transcripts. This example shows that these various subtypes, A through E, equally quantify using independently quantified RNA transcripts.

[Slide.]

One can also formally validate this with actual clinical isolates and not just RNA made in the laboratory. These are isolates provided by John Moscola's group and they were quantified initially by the P24 determination. Then we looked at the relative quantification using the actual assay across these subtypes and we see equal quantification of these genetically diverse subtypes.

at

[Slide.]

So I finally want to end with a clinical example. This is a patient who was cared for in Belgium who had a very low CD4 count--it is a little hard to see--and an initial viral load of close to half a million.

This patient was treated with an older regimen of sequential therapy of AZT which resulted in a modest reduction in viral load down to about 63,000. Then 3TC was empirically added with a further reduction in viral load to 2300.

Now, the selection of these drugs is not in keeping with the modern practice of using triple therapy but I show it mainly for an example of the differences in how the assays may perform with genetically diverse subtypes. In this particular individual, other assays were run. Amplicor and NASBA were run. They were either below the detection threshold of the assays at around 400 copies or just at the threshold.

It turned out that this particular individual had a subtype H, was from Central Africa and had come to Belgium for care. Again, this has to b placed in context. This particular example does not describe the systematic performance of the different assays with different subtypes.

It merely points out that with genetically

at

divergent isolates, you may get markedly different quantification results and the change in quantification that occurs with the initiation or change in therapies might be affected or interpreted differently depending on the assay results.

So I think, in summary, genetic diversity has to be looked at in the context of using these assays in diverse populations and that this has been the subject for a lot of research. Roche, NASBA and Chiron have all pursued looking at how these things affect quantification and improvements in probe design which will, hopefully, take care of this problem in the future.

Thank you.

DR. HOLLINGER: Thank you.

Any questions of Dr. Chernoff?

DR. NELSON: It was a very interesting and important presentation. Would you follow the data to suggest that if an assay were licensed as good for monitoring or following a patient's progress and making clinical decisions on an individual patient, or that it should follow that, at least for the Amplicor 1.0 or any other assay where there might be differences with genetic subtypes that the physician should know or test, determine the patient's subtype as part of the clinical follow up of

at

an indication patient?

DR. CHERNOFF: It is an important question. I think it really gets to the issue of if you see a patient who has a particular clinical presentation, like has advanced disease or HIV-associated symptoms or signs, has, let's say, a low CD4 count, yet the RNA value seems to be very discordant--in the particular example I showed, no RNA detected, but the patient obviously was ill.

It brings up two issues. One is the patient has, perhaps, a very pathogenic virus which doesn't have a very high particle count, which is a possibility, or that there is something wrong with the test.

The reason I pointed that out is that people are into the numbers games right now. They depend very heavily on the number and sometimes clinical judgment is pushed to the side. We hope that isn't the case. So, in those particular individuals, one could look at the epidemiologic group they come from; are they somebody who came from Malawi or Centra Africa and there is very high likelihood that this is going to be a non-B subtype or is it an individual who has some mutations in the region where the primers are directed which reduces the efficiency of the amplification reaction.

Routine subtyping of patients has not been done,

at

although HMA assays are available. Even the gel-shift assays may not detect a subtype because of the emerging diversity and they have to keep changing the probes that are used in those particular assays.

There are some serotyping assays that are available but they are not particularly good at routinely detecting the different subtypes. So I think one can consider that or use different assays, but it does bring up a clinical problem which needs to be resolved.

I think there are new probe sets that are being developed by the manufacturers which will, hopefully, take care of this issue.

DR. HOLLINGER: Any other questions from the committee? John, did you have something you wanted to add?

DR. SNINSKY: I just wanted to mention that in our advisory review in March of 1996, we presented data concerning the subtypes in our package insert. It speaks to the issue of subtypes that would be contraindicated for the existing assay.

As David mentioned, we, and others, have made a concerted effort to build a global surveillance program to identify isolates. Indeed, we are in clinical trials presently with an upgraded version of the existing test that has greater subtype range in terms of accuracy. It is a

at

complex puzzle that we are all dealing with globally because there is very little data in terms of how well the drugs work on some of these subtypes, let alone the diagnostics for monitoring them.

DR. HOLLINGER: Thank you.

The next presentation is by Mr. Michael Stocum from Organon Teknika.

MR. STOCUM: Before I begin my part, let me also say that Organon Teknika is actively working on improved primer sets for reactivity as well. I think, as Dr. Sninsky pointed out, it is a very complex, very involved process and we are working on that, also.

[Slide.]

First of all, I would like to thank the advisory panel and the FDA for allowing us to talk a little bit about some of our viral-load information that we have got. Today, I am going to talk about the effect of sample preparation on HIV-1 quantification and its relevance to monitoring these RNA levels in patients.

My presentation will be followed up by Dr. Christine Ginocchio showing some patient therapy data. She is from North Shore University Hospital.

[Slide.]

Just to make sure everyone is on the same page, we

at

look at amplification testing as four different steps involved with sample lysis beginning to open up and release the nucleic acid. The isolation part, which I am going to concentrate on in my discussion, subsequent amplification and then detection of the nucleic acid.

[Slide.]

In our nucleic-acid isolation, the aim of it is to purify the sample and remove any inhibitors to amplification. That should allow, also, the use of multiple sample matrices such as seminal fluid and others that might traditionally inhibit amplification.

A secondary effect is that you concentrate the nucleic acid. If you can allow for a larger volume input, you are able to generate a larger amount of nucleic acid which subsequently goes into amplification.

Lastly, you want to provide intact nucleic acid so that you can, indeed, amplify it with an end result, hopefully, of increased amplification efficiency.

[Slide.]

A study performed at GlaxoWellcome in Marty St. Clair's lab looked at five patients who were on triple therapy that included a protease inhibitor. It is very limited data at this point--again, it is five or six time points--but what it does suggest is that if you initially

at

take a smaller input of 0.2 ml, or 200 mcl, the possibility of quantification is relatively limited in that you are just above 50 percent for quantifiable results.

However, if you increase the volume on those patients that were not quantifiable, the end result is a much higher level of quantification. In fact, we were able to achieve 82 percent of the samples generating a quantitative RNA result.

[Slide.]

Translating that information into some more routine clinical work--I apologize for the small figures, but in order to get it all on the slide here--what we are looking at is five different sets of asymptomatic patients. Here in this first slide, we actually have a summary of ten patients who are asymptomatic and holding at a relatively viral load of around 4.0 logs copy per input. That is our first patient set.

The second patient set consisting of, I believe, nine patients actually remains stable and below the limit of quantification of this assay. Now, that is in contrast to others who initially may have had a steady viral load but a documented clinical-event-caused dropping of the viral load such as the initiation of drug therapy or the interruption

at

of drug therapy where this spike is observed here which then took the patient above that limit of quantification.

Non-compliance with a drug regimen also has an adverse effect on their viral load with a changing from a steady value down to a lower value.

So, with these background points in mind, I would like to introduce Dr. Christine Ginocchio, the director of microbiology at North Shore University Hospital to show some additional data on patient-therapy management.

DR. GINOCCHIO: Good morning. I would like, briefly, to present data from a study conducted at the North Shore University Hospital Center for AIDS Research and Treatment which assessed the clinical utility of measuring viral-load levels below the standard 400 to 500 copy cutoff.

By reducing the limit of detection to 100 copies per ml, using the NucliSens QT RNA assay, we hope to determine whether or not we could more reliably predict which patients were at increased risk for therapy failure and also assess how much earlier we could predict therapy failure which would then allow for a more rapid change from the failing regimen and finally provide an indication of a viral-load threshold goal that would hopefully predict a sustained response.

We monitored sequentially HIV-1 RNA levels in

at

34Êpatients enrolled in a protease inhibitor clinical-trial study from time periods ranging anywhere from 54 to 72 weeks. From these 34 patients, we picked a subset of 24 patients that had, through the course of their therapy, achieved viral-load levels under 500 copies by the comparator assay used in the clinical-trial study.

[Slide.]

This here is a summary of the data of the 178 specimens that were tested in the comparative analysis using the NucliSens assay with the lower limit of detection of 100Êcopies. Both assays had positive results in 111 of the specimens. 27 were negative by the 500 lower limit of detection of the comparator assay, and also negative at 100Êcopies with NucliSens.

There were 18 specimens negative by the comparison assay but positive by the NucliSens in the range of 100 to 500 with an increased detection level of 10.11 percent. There was an additional 22 specimens that were picked positive by NucliSens, negative by the other assay, for an increased detection of 12.36 percent.

In total, there were 156 out of 178 specimens that had correlative results for 87.64 percent. While the absolute numbers were different, the overall patterns of changes in response to antiretroviral therapy was highly

at

significant with a p-value of less than 0.0001.

It total, with the comparative assay with a cutoff of 500 copies, 62.36 percent of the specimens had detectable HIV-1 RNA levels. Using a lower limit of detection of 100Êcopies, we were then able to detect 84.83 percent positive specimens.

Overall correlation of the patient response to antiretroviral therapy was then looked at as far as what was the clinical significance of being able to detect higher levels of positive specimens using a lower limit of detection. The increased detection rate provided us with the following relevant clinical information.

[Slide.]

What we found was that there were ten patients with reduced but detectable HIV-1 RNA levels between 100 and 500 copies that eventually had a sustained rebound in viral load in 13 separate occasions. Earlier prediction of this rebound, when you are simply able to change the detection limit from 500 to 100 copies in three patients, one month sooner, four patients, two months, three patients, three months earlier, two patients, five months earlier and one patient, six months earlier.

One of the patients had a sustained HIV-1 RNA level below the 100 copy for over 19 months duration.

at

[Slide.]

Some examples of following the trends in these patients is shown on the next slides. Patient CP was started initially on a protease inhibitor and one RTI, had levels that went below the 500 copy cutoff but not below the 100, and then had a sustained rebound in viral load that was not altered until the second RTI was added on to regimen.

Again, here, the patient is undetectable below a 500-copy cutoff but never made it below the 100 copy which then, again, was predictive of a sustained rebound in viral load.

[Slide.]

In patient JCS, again, there were two points where the patient went below 500 and, in this one case, below 100 copies but only for a one-month time period. Again, a sustained rebound, significant in viral load that was then reduced by the addition onto two RTIs to the protease inhibitor.

Again, here, the patient only went down below the 100 detectable copy level at one time point and then rebounded to detectable levels which were sustained. By using a 500-copy cutoff of the comparator assay, the patient was considered negative for over six months while we had detectable HIV-1 RNA levels.

at

[Slide.]

Patient JCM was one of the patients that had an exceptionally good response to the protease inhibitor in combination with one RTI and then when two RTIs were added on in the second arm of the study. What is significant about this patient here is that what is the actual copy number of this patient that is below the 100 level detection.

This is what we are looking at now. In trying to get some idea as to what the actual threshold is--perhaps it is going to be eventually zero--but this will give us some more information as to why this patient appears to be a responder.

The other point is that, in being able to measure levels to a much lower degree, you are also able to get a better idea as to what is the slope and the response of the patient. This may also be an indication of what the long-term prognosis is and response to different antiretrovirals.

[Slide.]

So, in summary, what we found was that failure to reach sustained HIV-1 RNA levels below 100 copies per ml was suggestive of eventual failure and the ability to measure HIV-1 RNA levels to a lower limit of 100 copies greatly

at

enhances the ability to predict therapeutic response.

I think what we definitely need is accurate viral-load assays with detection limits even below 100 copies which would be essential for monitoring response to antiretroviral therapy and to allow earlier intervention for failing therapy.

Thank you.

DR. HOLLINGER: Questions from the committee?

I noticed your last slide which shows a line going across 100. Really, if that is your lower limit, it really should go below that line because it suggests that you have got a positive response at 100.

DR. GINOCCHIO: It is actually below the 100.

DR. HOLLINGER: It is really below, and what you are saying is that you don't know where it is. It could be zero.

DR. GINOCCHIO: Exactly. It could be zero.

DR. HOLLINGER: Or it could be positive.

DR. GINOCCHIO: Right.

DR. HOLLINGER: But I think the point is well taken.

DR. NELSON: I guess you have studied longitudinally for a long time a limited number of patients, and there are still a lot of questions as to what under 100

at

or under 400--I think the critical question is when people fail from a level that is even zero, do they rebound as quickly as if they were rebounding from 400.

There are some data, I think, that suggest that, at least over the first three or four years of therapy, that that is the case. If that is true, then we still don't know what it means if the level is 400 and the patient is asymptomatic and doing well or 100 or even 10,000 or undetectable with a lower cutoff of 100.

So I think that there are still some questions that will need to be answered in terms of what an individual level or response means in terms of the prediction for that patient or for a group of patients over the long term.

DR. GINOCCHIO: I think it is very important. We just, right now, don't have that information because, in general, the assays don't go to lower limits to detection below 100 copies. But this will be important as we learn more about response to antiretrovirals and being able to assess, is the patient going to have a long-term response to the therapy that the patient is currently on.

DR. HOLLINGER: Did you do proviral DNA on these patients?

DR. GINOCCHIO: No, we didn't.

DR. HOLLINGER: To see if there was any virus

at

present? Or did you do any cultures?

DR. GINOCCHIO: No. We didn't do cultures at this point.

DR. HOLLINGER: Thank you very much.

Is there anyone else during the open public hearing that wants to speak to any of these issues? In that case, I think Dr. Smallwood would like to make a comment, first of all, about the committee and why it is sitting.

DR. SMALLWOOD: Before we proceed to the committee discussion and recommendations, I would just like to advise everyone here that the Center for Biologic Evaluation and Research has a regulatory responsibility for certain medical devices which, according to their use and/or manufacture, may be related to the mission and area of expertise found in CBER.

While the product that is under discussion today is an in vitro diagnostic, it has been reviewed by CBER and, thus, has been brought before this committee. According to 21 CFR which is the Code of Federal Regulations, Part 800, a PMA or premarket approval application or 510(k) or a substantially equivalent product may be brought before a medical device panel.

A medical device panel may be asked to recommend approval of an application or provide advice or consult on

at

specific issues of performance or label claims. Today, the Blood Products Advisory Committee will sit as a medical-device panel according to its charter to consider a labeling change submitted as a PMA supplement.

Accordingly, this panel, then, will be asked specific questions related to this supplement for which it will, hopefully, provide responses.

Thank you. Are there any questions concerning the role of the panel at this point?

Presentation of Questions

DR. HOLLINGER: I think we should put up the questions, if you would, please.

DR. DAYTON: Let's see if we have better luck today.

[Slide.]

Number one, should the FDA approve labeling of the Roche Amplicor Monitor Test Kit as an aid in management of patients on antiviral therapy for HIV disease.

[Slide.]

Number two, if not, then what additional claim, if any, is appropriate for the Roche Amplicor Monitor based on the current submission.

DR. HOLLINGER: Thank you.

Committee Discussion and Recommendations

at

DR. HOLLINGER: As a committee, then, let's deal with the first question about should the FDA approve labeling of the Roche Amplicor Monitor Test Kit in the management of patients on antiviral therapy for HIV disease.

DR. MATHEWS: Could I ask a question? In answering this issue, is it the agency's intention that the primary judgment has to based on the clinical trials submitted by the applicant or is the committee allowed to take into account the aggregate information that has been presented in the packet that we have received and other information presented today?

DR. SMALLWOOD: Dr. Tabor, do you want to respond?

DR. TABOR: I think, technically, we have to rely on what is in the submission. But we would like your opinion of the issue of management versus monitoring versus prognosis with regard to the data you have seen today.

DR. LINDEN: Does FDA have specific criteria that must be met to meet such a claim? When Dr. Dayton spoke originally, he sort of implied that was the case but those criteria have not really been supplied to us.

DR. DAYTON: I may be overruled. I think, in internal discussions, what we are looking for here is if there is a reasonable subset or group of patients within a reasonable set of parameters for which reasonable management

at

can exist based on a submission, then you would, in a most narrow sense--you could give them a claim for a very narrowly limited set of parameters and you would expect to see the enlargement of that use based on the postmarketing studies.

We don't have really hard and fast rules on this particular issue as to whether you have to have a Rolls Royce of management protocol such as a real switching therapy. I think the bottom line comes down to what the committee has discussed in the past which is, if you are a physician and you are in the clinic, is there a situation in which you get these results and they are useful to you.

Does that answer your question?

DR. LINDEN: Yes; I think so. Thank you.

DR. STRONCEK: That confuses me a little bit because, as I am a transfusion-medicine person and trained in clinical oncology. My understanding of this situation is that this product is approved and it is in the clinics and it is available to any clinic that wants to use it. Basically, once they buy it, they can use it for what they want.

But if it is labeled--labeling has marketing implications to me. If something is labeled as a diagnostic, that's one thing. But if we are going to label

at

it to manage it, that means the company can market as a management tool. To me, then, the data better be pretty good. That is kind of a warranty claim on that label.

So I would not feel comfortable voting for adding something on the label of a product unless the data very solidly backs it up unless, of course, this product would otherwise be non-available to the patients. But, for products available to the patient already, I think that data has got to be pretty solid to change the labeling.

DR. KHABBAZ: The difficulty that I have, although I agree with you, is that we have a standard of care that has been defined by the guidelines, the HHS guidelines, that, in actuality, call for the use of monitoring for decisions for management.

I guess I sit here thinking, basically, what is the importance of changing a label. Who is it important to; to the treating physician or the patient? The standard of care has been defined by another body. Adding the label, the value? Maybe somebody can clarify this. Who is it benefitting?

DR. KADREE: I sort of have the same question. Perhaps what might help to clarify is what are we defining as monitoring versus management because I think there is a very fuzzy line. I think if you are using a test to monitor

at

how a patient is doing, then you are using it in their management. So I am not sure exactly what distinction we are really trying to make.

DR. HOLLINGER: I, personally, don't have any problems with approving the labeling as an aid in the management of patients on antiviral therapy or, as they have it, in the thing which I would probably leave out, by serial measurement, necessarily, whatever that means, just to monitor the effects of antiviral therapy during the course of antiretroviral treatment.

I think it is being used for that and I think it has a real benefit in that. But there are some issues I have. I do not think they are at a level right now where you can predict. This is all group data. You can't look at an individual and say to that individual, "Because you have this level, this is exactly what is going to happen to you."

You can say, as a group, this is what we expect. But for the individual patient--we have the same problem with hepatitis C in that we know certain patients that have a certain level will not respond as a group. But there are people in that group who are cured and there are other groups which we say most of these patients will have a response. But there are people in there who will not have.

So, I have problems with that kind of an issue,

at

particularly when you say that there is a 30 percent, reduction, for example, at 16 weeks. That is not a lot. That means 30 percent will have a reduction, but there is 70Êpercent that will not. And we don't know at what level, and so on.

So I do think that the RNA tests are beneficial in the management of patients in making treatment decisions. I don't think we have enough information. We know that if is zero or undetectable, that is important. But, outside of that, I am not sure what it does mean. I think there is a gradation.

If you don't respond, then that is probably indicative that you are going to progress.

So, as I said, for myself, I don't have a problem with it. I would just sort of broaden it then to almost make the statement much what the FDA had recommended, as an aid in the management of patients, and sort of let it go at that for right now until there is more information.

Maybe this will stimulate some of the committee to wake up now.

DR. NELSON: It is very complicated. I think that in an individual patient, we don't know what the difference between 400 and 100 is. But we do know, even for an individual patient, if they have 5 million copies and

at

nothing happens to those copy numbers with the drugs that they are treated with that their prognosis, in general, is not good and the average physician should know that and should change therapy based on that result.

But if the numbers go from 5 million to 100,000 and stay there--in other words, overall there is usefulness, some utility, in monitoring, but the exact numbers, even over and above the variability of the assay, the exact numbers even beyond the variability of the assay are not well known in terms of the long-term prognosis; not only the long-term prognosis, but what should the physician do in terms of giving them another drug that might cost them $10,000 a year.

I think that is an unknown at the moment, but I think there are categories where viral load is clearly an aid in managing the patient. But it is not as tremendous an aid in each individual patient as, perhaps, a label could imply that it might be. That is the dilemma, I guess.

DR. HOLLINGER: I think you are right. That is why I kept asking often about real time or batch testing. Batch testing is, obviously, the best way of doing anything and we are often able, because we save specimens, to go back and compare baseline with something.

That is probably the best way, as you all know,

at

with doing most testing. But in most cases, this will be used as real-time testing. I am very reluctant, personally, in most PCR tests, to give much credence to a change that is less than five-fold, although I would consider a three-fold.

So if it goes from 100,000 to 20,000, I think that may be important. If it goes from 100,000 to 50,000 I would consider that that is certainly within the realm of the testing and that doesn't mean much. The patient will look at that and say, "Gee, look; I am really doing well."

Then, the next time he comes it, it is 200,000. He says, "My god, I am getting worse." It may not have any differences whatsoever. So I think that is something we need to take into account.

DR. MATHEWS: One of the questions that was asked a few minutes ago is what is in it to expand the claim once the product is already available. I think it does have real-world impact in that payment for more frequent monitoring is not uncommonly linked to what the label says on the part of various insurers and third-party payers. From our own clinic, we see that all the time.

So I think that is important. One of the, I think, dilemmas in the way that the question is framed is that we haven't really spent, and probably nobody has, a great deal of time considering what are the criteria of a

at

useful tool for patient management.

I think if you narrowly focus it on requiring absolute predictability, it will be way off target, that one of the major things that I think of as a useful tool to manage is does it reduce uncertainty about the likelihood of a successful treatment.

In other words, what I have the patient on, will I be more confident that I am either doing the patient a good job or a bad job based on new information. I think that other dimensions to that include will the information that I gain from monitoring lead to more successful outcomes or will they also, perhaps, lead to withdrawal of therapies that are not benefitting but are producing toxicity.

All of these are dimensions of patient management that any candidate test could pertain to.

The last point I want to make is that, in the real world, to address these questions, there are very limited opportunities. These windows open up in the course of HIV disease over time where you can study something and then, if you don't study it right then, the window is closed and the question can't be answered except by retrospective analyses of various datasets.

I think that the data that Dr. Haubrich presented represents a remarkable example of taking the opportunity to

at

look at a window. I was very skeptical that that study could be completed but, thank goodness, it was done. I think the results are incredibly germane to the question of patient management.

DR. GATES: Just coming from the device side, to my mind, the product is a test that is an adjunct to a whole range of other information and the physician is going to have to make a decision. So the question is is the test accurately reflecting what is happening in the patient and is that predictive of what is going to happen in the future.

It seems to me that I have to agree here that it is a case where what you are trying to do is reduce the amount of uncertainty to the extent that this does, then I think you have to incorporate what is saying here, part of the ongoing patient management but just as a tool to determine that, basically.

DR. HOLMBERG: I think that the data that was presented today basically only gives me enough information to say that it is a device to monitor and not necessarily management. I think, though, that the clinician has to make the determination whether to use the results for the management and that is the clinician's prerogative.

I think that anything stronger than an aid in management, we do not have the data to support that. So I

at

do support the way the question reads, as an aid in management of patients.

DR. MITCHELL: I have a question as to whether we should state in there a caveat saying if there is a five-fold change in the results, then we can use it.

DR. KADREE: I guess this question is for the FDA. This test is already being used as a management tool so I am not sure why we are trying to--what is the distinction that we are making at this point because monitoring someone's viral titers and using that information to treat is using it as a management tool.

DR. HOLLINGER: Ed, can you answer that?

DR. TABOR: The distinction between prognosis, monitoring and management was crafted, in part, because of the limitations of the data that were available at the time of the original approval.

I think that we can have some flexibility now in terms of using these distinctions. I think that we should realize that, to the physician reading the label, the exact wording may not mean the same things that it means to a regulatory body.

It certainly means something to the company to have the labeling changed. I think that point has been made correctly already. But I think there is room for

at

flexibility and that is one of the reasons why it says aid in management instead of management here.

I think the committee can recommend flexibility if you want.

DR. VERTER: I spent a while last night trying to go through all these numbers. I must confess I was very confused. I think I finally got most of it. Dr. Miller's presentation helped and Dr. Flyer's actually helped a bit more. But I think I share the general sense that I am hearing that the word "aid" is fine, but my concern is what happens when you do that and what claims will be made.

What I found, both from reading the literature that was provided to us in the packet and from both statistical presentations today is I am unclear how to estimate the effect. There were just too many numbers and the right numbers, at least for me, weren't there.

This is something that maybe the FDA can take back, Dr. Flyer working with the company or by himself or with others can try to assess. But there were constant issues to me of numbers varying between tables, missing data, values being carried for 8, 12, 16 weeks which, to me, could have a significant impact on estimates, not necessarily the sense that it wouldn't be an aid.

But if we are going to try to say that there is an

at

x percent reduction for a two-log or a five-log difference, that is where I am kind of concerned, that we go too far. So I don't know what the implication is of voting the statement as it is, which I am tending to say, okay, fine, we can do that.

What happens once that occurs? Do they have free reign to go out and use the analysis in some of these estimates? Then I would be unhappy because I don't think those models correctly estimate, or I am not sure they correctly estimate, the impact.

Just one closing remark. Also, it was unclear to me specifically once you had the baseline, what week 4 added or week 4 and 8, or just week 16. It is all those permutations that were unclear to me. Maybe just one more measure is necessary. And, of course, the cohorts change over time.

DR. DAYTON: Can I answer part of that question for the FDA? I don't know effective it is, but we do have the authority to control the use of this by appropriate labeling. And we can. If you feel certain usages of this should be restricted, we would appreciate advice on that and we can certainly incorporate that in the package insert and in the labeling. So those issues can be dealt with in that manner.

at

DR. HOLLINGER: I think that you have heard some of the concerns about prediction and so on at this time.

DR. STRONCEK: The only comment--studies were very nicely shown that by measuring levels of HIV-1 RNA, you can treat patients and maintain low levels of RNA for long periods of time. But it is still unclear to me how predictive that will be for good patient outcome.

I think it is worthwhile to vote. I agree that this can be used as an aid in the management of patients with HIV therapy, but I still we still be cautious to remember that this is still a surrogate and the ultimate thing, that goal, is to improve clinical survival and this is just a kind of an intermediate marker in that goal.

DR. HOLLINGER: A call for the question. Read the question here and then let's vote on it. The question is, should FDA approve labeling of the Roche Amplicor Monitoring Test Kit "as an aid in management of patients on antiviral therapy for HIV disease?"

All those that agree or vote yes on that question, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[No response.]

DR. HOLLINGER: Those abstaining?

at

[No response.]

DR. HOLLINGER: We will ask our consumer rep, Ms. Knowles.

MS. KNOWLES: I agree.

DR. GATES: I agree.

DR. VERTER: I voted yes and I must confess, after the statement I made, I was a little reluctant. I really hope, and I know Jay has heard this before, that the FDA has heard what we have said, or maybe just what I have said, that you look carefully into what the implications are for labeling.

DR. HOLLINGER: Please read the vote.

DR. SMALLWOOD: There are 14 members here today that are eligible to vote. The results of voting; there were 14 "yes" votes. There were no "no" votes, no abstentions. Both the consumer and industry rep agreed with the "yes" votes.

DR. HOLLINGER: We are going to adjourn for lunch and then come back. But before we do, and I will probably say this again some time in the future, but I want you to know that the committee here, for sure, at least myself, is appreciative of the efforts of people who come and speak here even though there is no applause. That is not part of it.

at

The fact is that we are all appreciative of the things that you bring us to look at and for the presentations, that would be true for this afternoon, also.

We are going to adjourn until 1 o'clock. At that time, we will start with the discussion on HCV risk in sexual partners.

Thank you very much.

[Whereupon, at 11:30 a.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

at

A F T E R N O O N P R O C E E D I N G S

[1:05 p.m.]

DR. HOLLINGER: This is open, mostly informational. I am sure it will come back to the committee in the future for some possible action. So it is mostly to help everyone sort of understand what the issue is so that we can act on it in the future.

So we will start out on HCV risk in sexual partners. The first will be an introduction and background by Robin Biswas.

HIV RISK IN SEXUAL PARTNERS

Introduction and Background

DR. BISWAS: Thank you, Dr. Hollinger

[Slide.]

The issue that I am introducing to you this afternoon is whether or not the sexual partners of persons with a positive test for antibody to hepatitis C virus should be deferred from donating blood.

The reason that we are bringing this topic to the committee is because some blood-collection establishments submitted SOPs to the FDA permitting or excluding partners of anti-HCV-positive persons from donating.

[Slide.]

Now, the Code of Federal Regulations, which I have

at

up there, states that persons should not donate if there is a history of close contact within six months with an individual having viral hepatitis. I should add that, in April of 1992, FDA distributed or released recommendations increasing that period to one year.

Now, these regulations were mandated in the early 1970s before there were sensitive tests for hepatitis B virus, meaning that there really were no RIAs, EIAs, available for hepatitis B surface antigen. It was two years before testing HBsAg testing of blood was mandated by the FDA and that occurred in 1975.

Of course, it was nearly two decades before there were any tests for hepatitis C.

[Slide.]

So, because of this, the term "viral hepatitis" in the Code of Federal Regulations has been used to signify clinical hepatitis or jaundice and did not refer to positive tests for viral hepatitis. When we went over written statements in technical, in particular the ABBA technical manuals from the 60's and 70's more recently, it is quite clear that the term viral hepatitis means clinical, symptomatic disease.

In order to be able to decide an appropriate FDA position regarding this issue, how to manage the sexual

at

partners and spouses of persons who were anti-HCV positive, the question of whether or not HCV infection is sexually transmitted needs to be addressed.

This afternoon, we will be hearing from three scientists; Dr. Kathy Cantilena from the NIH, Dr. Sherri Stuver from the Harvard School of Public Health, and Dr. Miriam Alter from CDC. They will present data from studies involving spouse or sexual partners of individuals who are anti-HCV positive or have HCV infections.

It may be possible for the committee to draw some preliminary conclusions. However, we are not requesting committee recommendations this afternoon for several reasons. First, it was not clear before the meeting whether sufficient scientific data from studies would be available for presentation.

It was also thought desirable that the committee should have sufficient time to consider the scientific information. As Dr. Hollinger has said, this issue will be brought before you again sometime in the future.

Thank you very much.

DR. HOLLINGER: Thank you, Robin.

The next speaker on spouse studies will be Miriam Alter from the CDC.

Spouse Studies

at

DR. ALTER: Thank you. I somewhat ruined my reputation by providing you with hard copies of my presentation ahead of time--not much ahead of time but ahead of time. So just to make sure that I hadn't completely ruined it, I snuck in a slide in my presentation that is not in your packet. That way, you will have to pay attention and keep your pencil handy.

[Slide.]

I wanted to do two things today. I wanted to address the specific issue of transmission between spouses or partners, individual partners. But also I wanted to present a little background on the evidence for transmission of HCV in general because I think, one, to address this issue, we have to decide, or at least understand, the evidence for sexual transmission of this virus which is still somewhat controversial.

You are all pretty much familiar with the traditional risk factors for HCV transmission as shown on this slide, most of which are primarily direct percutaneous exposures to blood with the addition of what we assume is mucosal exposure in the perinatal setting.

What we are dealing with today is the evidence for sexual exposure to an anti-HCV or HCV-infected contact and a little bit, as I mentioned, the evidence for sexual

at

transmission that we glean from populations with different sexual behaviors such as those with multiple partners.

[Slide.]

The strongest evidence for sexual transmission of HCV actually comes from case-control studies that were performed prior to the discovery of this virus when we just called this non-A/non-B hepatitis. These studies were done--there are two studies both of which were done in patients with acute non-A/non-B hepatitis, one of which was done in Baltimore in the late '70's and early 1980 among outpatients and inpatients identified at five acute-care hospitals with acute non-A/non-B hepatitis.

Controls were patients seen for non-traumatic conditions with certain matching criteria seen at the same place of treatment who had no evidence of hepatitis at the time.

The second case-control study was done in two of the sentinel countries that we have at CDC in the mid-1980s among cases of community-acquired acute non-A/non-B hepatitis reported to country health departments who had no histories of transfusion or injection drug use in the six months prior to onset of their illness.

Two controls per case were selected by random digit dialing. They had to have normal ALT levels and,

at

themselves, no history of transfusion or injection drug use.

[Slide.]

In the Baltimore study, you will note that we found that, in addition to the what I will call traditional percutaneous risk factors, we found that sexual or household contact were associated--that cases of disease were significantly more likely to have a sexual or household contact with an individual who had hepatitis than were controls.

For the purposes of presentation, the sexual and household were put together. But I can tell you that in the original study, these were independently associated with infection. Together, they had an adjusted risk of about 20 compared with their controls.

[Slide.]

In the sentinel country study in the mid-1980s, we found, in addition to sexual or household contact which, in this study, again, we combined for the purposes of presentation, but, because of the small numbers, they were not independent of each other in the original study.

We also looked at multiple sexual partners which we had not looked at in the Baltimore study. In this study, in the absence of a history of transfusions or injection-drug use, or any other percutaneous risk factor,

at

having multiple partners in the six months prior to onset was a significant risk factor among cases compared with controls.

So this was probably the strongest epidemiologic evidence that we have.

[Slide.]

Then the discovery of hepatitis C virus came along and a large number of seroprevalent studies were reported in the literature that attempted to evaluate sexual, household and perinatal transmission. For the purposes of this presentation, we are only going to be discussing sexual.

But we have to take into account that there are many limitations to the studies that have been published, particularly in terms of addressing whether or not sexual transmission takes place. Inadequate sample sizes; if this is a very low frequency event, most of the studies that have been conducted do not have sample sizes adequate to even address the question.

Many of them did not take histories of percutaneous risk factors on their study subjects and, therefore, you are not able to distinguish between what might be a sexual risk and what might be a risk from injection-drug use, for example.

Many, of course, of the original studies were done

at

with first-version screening tests that are not as sensitive as our current versions. Some studies didn't use supplemental assays to rule out false positivities. Incomplete follow up was not an issue for the sexual studies and, of course, study methodology differs so dramatically between studies that it is sometimes difficult to compare them.

[Slide.]

One way, of course, we can look at whether or not sexual transmission takes place is to look at populations with different sexual behaviors. What I have done is summarize studies that have been done in three populations; men who have had sex with men, heterosexuals attending clinics for sexually-transmitted diseases, and studies performed among female prostitutes.

I have used only studies that use supplemental assays to rule out false positivity and only those studies which took complete histories of percutaneous risk factors and excluded those individuals from these calculations. The average prevalence of anti-HCV among these populations ranged from about 3 to 6 percent with fairly broad ranges between studies.

Risk factors, in spite of these relatively low prevalence rates, associated with positivity included

at

increasing number of partners, not using condoms, having a history of other sexually-transmitted diseases, the duration of high-risk sexual activity and even sexual activities involving trauma.

In one of the studies of female prostitutes, however, the number of partners you had before reaching statistical significance, as it were, was something like 10,000, not exactly a number you can extrapolate to the general population.

People, you are asleep. Someone laughed? I just didn't hear it?

[Slide.]

Going on now more to the studies of partners of individuals who are anti-HCV positive, this slide summarizes studies, again, which employed anti-HCV EIA with supplemental testing and supposedly excluded contacts who had other risk factors for infection.

I have also divided these studies by geographic areas because the differences in prevalence rates between the geographic area and because you will be hearing, actually, some of this by another speaker. But you will note that if you look at the prevalence of anti-HCV positivity among the spouses of individuals with chronic hepatitis C in some of the Asian studies, we find that the

at

average is about 25 percent, which is really quite high although there are quite a few studies that found no positives among the partners.

But note that the number of studies are relatively few and that the number of subjects studied in each of the projects was also relatively few. If you had a transmission rate that was only about 1 percent, for example, and I am just using that as a hypothesis, you would be unlikely, in most of these studies, to even see any transmission. I think that is something we have to take into account.

In only two studies were control populations used so that they could compare infection rates among the partners of patients with chronic hepatitis C to the partners of those with no evidence of hepatitis. Again, the average prevalence was not all that different in many of these studies. It was about 2 percent even in the control partners.

In studies performed in the United States, Western Europe and Australia, the prevalence of anti-HCV positivity among spouses of patients or partners of patients with chronic hepatitis C averages about 5 percent with a range of 0 to 15 percent. In the United States, the number of studies done have been so small and so few that virtually all of ours, at least published, have found no evidence of

at

transmission in spouses.

In those studies that have looked at HIV-coinfected individuals, there have been quite a few studies that have demonstrated transmission only from partners that are coinfected. But, again, the average prevalence in these studies is similar to partners who have HCV alone.

Again, we don't see a real difference between other household contacts. It doesn't mean that this virus is not transmitted between partners.

[Slide.]

There has been one very nice study published by Dave Thomas and colleagues from Johns Hopkins which looked at the partners of STD patients who were identified as being anti-HCV positive. This study found that among male patients who were anti-HCV positive compared with male patients who were anti-HCV negative, the status of their female partners was no different; that is, the prevalence of hepatitis C infection among female partners did not seem to affect the prevalence of HCV infection among the male patients.

However, female patients who had a positive male partner were four times more likely to be positive than female patients with a negative male partner. So this

at

suggested some evidence that male-to-female transmission was more efficient than female-to-male transmission.

[Slide.]

He then looked at both the presence and titer of HCV RNA among the male/female partners in which apparent transmission seemed to take place and a random sample of HCV-RNA positive males were not implicated in transmission. As might be expected, he found HCV RNA in most anti-HCV positive individuals, as we well know.

He did not find a significant difference in the titer between men who appeared to transmit to their female partners and men who did not because there was considerable overlap. He did find, however, the male/female partners between whom transmission seemed to occur had a might higher degree of sequence homology in the NS5B region than did randomly selected men when they were compared to each other.

However, we now know that this particular region of the genome may not be heterogeneous enough for us to draw strong conclusions about this.

[Slide.]

This is my surprise slide. As I was sorting through my slides, I had actually forgotten that we had done a preliminary analysis of two of our ongoing studies, as you can see, a couple of years ago. We have not updated it

at

since then, but the first study group are anti-HCV positive pregnant women who have been entered into a study to look at the risk of perinatal transmission from them to their infants.

This is an ongoing study and we are just closing out enrollment of about 300 of the women. But, at the time we looked at this, we were looking at, also, their sexual partners and other household contacts. We had tested 64 of their sexual partners and found that 19, or 30 percent, were anti-HCV positive. 17 of these 19 had other risk factors for HCV infection. Two did not.

The other group of individuals we have been looking at were patients with sexual partners of patients with chronic hepatitis whom we have been following since 1985. Seven of the 18 that we had tested to date were anti-HCV positive for a prevalence of 39 percent. Four of those seven had other risk factors for HCV infection and three presumably did not.

We also tested 92 spouse sexual partners of pregnant women who were anti-HCV negative; no, sorry. Of an additional 92 women who were anti-HCV positive, we tested their anti-HCV negative sexual partners by PCR for HCV RNA to determine whether or not we were missing any infections in the spouses because of the sensitivity of the test.

at

At least, of those 92 anti-HCV negative partners, we did not identify any PCR positives. But the sample size is a bit small to make any solid conclusions.

[Slide.]

If we look at patients with acute hepatitis C who have been identified during the last five years in our sentinel surveillance project, and I presented this, I think, the last time I was here, about 15 percent of these patients give a history of an exposure to a sexual partner who had hepatitis or to multiple partners.

In two-thirds of these, the sexual partner was anti-HCV positive and the index case had no other risk factors for their infection. We will be looking at this further, hopefully doing some molecular studies to look at how closely related the viral isolates are of these partners.

[Slide.]

Again, when looking at exclusion of individuals, it is nice to know how prevalent the characteristic as well as the infection is in the general population. Again, this is a slide that I showed you last time when we were discussing another issue.

As you can see, in terms of the prevalence of partners of individuals infected with HCV, we have no idea

at

how many there might be in the population nor in the United States do we truly have a good idea of what the prevalent of infection is in these individuals in the absence of other risk factors.

At the moment, the studies are too few and too small for us to draw any strong conclusions about what the risk might be.

[Slide.]

So if we are to summarize what we know about sexual transmission about HCV, it is pretty much what we knew, I would say, five years ago. In my opinion, sexual transmission of HCV does occur, but the efficiency is very low in this setting. Unfortunately, we can't quantitate the risk because we don't have enough data so what we usually say is that it is rare but not absent between long-term study partners.

But because we are unable to quantitate the risk and we don't even know what factors are related to transmission, it is extremely difficult to counsel individual patients or to make recommendations about the risk in different settings.

We do know that sexual transmission appears to be more frequent among those with high-risk sexual behaviors, patients who have had a history of other SDTs and

at

individuals with multiple partners.

[Slide.]

When we counsel individual patients about the risk of transmission, currently the Public Health Service does not recommend any changes in sexual practices for individuals with steady partners. We do recommend that these individuals be informed, that sexual transmission is possible, so that they can make some decisions, hopefully along with their partners, about whether they want to use any precautions.

Obviously, with an individual with multiple partners is supposed to be practicing safer sex, not only for their protection but for the protection of other individuals to prevent many sexually-transmitted diseases and not just in relationship to their HCV status.

That's it. Thank you very much.

DR. HOLLINGER: Thank you, Marian.

DR. MITCHELL: Do you have any evidence about the amount of virus that might be in other bodily fluids like vaginal or semen? Do you have any information about that?

DR. ALTER: No, but--did you keep my carousel on there? Funny, you should ask that question. I wasn't going to show this slide unless someone asked the question.

[Slide.]

at

We tried to summarize the studies that have looked for HCV RNA in a variety of other body fluids, but particularly semen and vaginal secretions. You can see that a variety of studies have been done. So we summarized them based on whether they found anything or they didn't find anything.

You can see that there has been one study that did detect HCV RNA in semen in four of 17 individuals. There have been two studies that detected no RNA in 18 individuals. In both of these studies, individuals had chronic hepatitis C. There has only been one study of two women looking for HCV RNA in vaginal secretions and it was a negative study.

There is, at least to my knowledge, no attempt to look at titer, although I don't know what even that would mean at this point in time. But there it is. That is not in your packet either.

DR. NELSON: I guess Dave Thomas' study might suggest that SDTs might affect the transmission but, clearly, that has been well studied or fairly well studied with HIV and a little bit with, I guess, hepatitis B as well.

Are there any data on the influence of an STD in the risk of transmission or the levels of virus or anything

at

like that? In other words, might it be that some of the--

DR. ALTER: Lesions; the presence of lesions?

DR. NELSON: Yes; that some of the studies between stable partners where there was no STD, there was little transmission, but in some where the risk was amplified by an inflammatory process such as an STD that the risk was elevated. I don't know if there are any data on that.

DR. ALTER: I, at the moment, can't think of any studies in which they have actually--like they have for HBV, for example, where they have actually observed lesions, they actually studied individuals and looked at lesions in relationship to their acquisition of HBV infection. This was primarily among men who have sex with men.

I am not aware of any studies that have looked at that. Someone else might. Again, the finding of a higher prevalence with a history of STDs is fairly consistent. What is not consistent is what STD they had in the past. In other words, it is not always syphilis, it is not always gonorrhea. Sometimes it is herpes, sometimes it isn't.

DR. NELSON: That is all confounded by a lot of other things.

DR. ALTER: Right.

DR. NELSON: Numbers of partners, socioeconomic status, where you recruit, because you have shown lower

at

socioeconomic status is--

DR. ALTER: Consistently associated with this infection.

DR. NELSON: And the STD clinics where patients are recruited. It is all sort of entangled.

DR. ALTER: Even Dave Thomas says that he is never sure that he has excluded all drug users from the population. He can never be sure. He does it to the best of his ability, probably does it better than most people. But he is never positive and so he doesn't know how much that might be--

DR. KHABBAZ: Miriam, I had a couple of questions, actually a comment and a question on that one, to the variant efficiency of transmission, male-to-female versus female-to-male. We observed that with HTLV1. Of course, there, the virus is cell-associated and that kind of explained it to some extent.

When one looked at the viral titer, and I see that you have a difference, as well, with even viral titer. It was significant, basically, in one study that had high viral titer transmitted it more efficiently. Was the difference significant here?

DR. ALTER: You are talking about in Dave Thomas' study?

at

DR. KHABBAZ: Yes.

DR. ALTER: But it wasn't significant, actually.

DR. KHABBAZ: It was not. So that is different.

DR. ALTER: There is a trend but, as he points out, there is such overlap between the two groups that--

DR. KHABBAZ: So there was not. Also, your comment on when you looked at--I forget; I think this was the mother-to-child study. You said some of the male partners were positive but they had risk factors, other risk factors. 17 of 19 had other risk factors. Was this a cross-sectional study and are you dealing with male-to-female transmission where the male partner had the risk factor?

DR. ALTER: This is a cross-sectional study in which we are identifying pregnant women who are anti-HCV positive in order to follow their infants from birth. So we identify their male partners at the time we identify the women.

DR. KHABBAZ: So it is a one-time testing of the male partner.

DR. ALTER: It is a one-time testing of the partner--is that what you asked?

DR. KHABBAZ: Yes; so finding a risk factor in the male partner doesn't really--

at

DR. ALTER: Right; you don't know which way the transmission went. That's correct. But in terms of one of the discussions that we have had in the group here is can you identify an anti-HCV positive individual based on their risk factor so that you can exclude them before they ever even--at the time of donation, they would be excluded because they had other risk factors, not just the anti-HCV positive partner.

DR. KHABBAZ: The other question relates to the table that you show differences in, possibly, rates in partners in Asia versus I guess Western Europe and Australia. Are there differences in strains that might account for that?

DR. ALTER: I don't know that there are sufficient differences that would account for this. There is no evidence that different strains are transmitted at different rates. I think there are cultural differences and there are differences in events that occurred in the community that may have accounted for these higher rates, and that is probably going to be discussed by a following speaker.

But a good example, and if I am stealing your thunder, I am sorry, is a study that was done among spouses in Japan that showed an increasing rate of infection with increasing duration of marriage.

at

The problem, among other things, was that those individuals with the highest rates of infection were those married 50 or 60 years and those with the lowest rates of infection--in fact, almost no infection--were those married less than ten years.

Do I dare make a joke? One would assume the frequency of sexual activity does not go up with the duration of the marriage. One would presume that frequency during the first ten years would be more likely to cause transmission than frequency after 30 or 40 years of marriage.

There has also been a lot of discussion since those studies were done about risk factors that may have been common to the spouses, that occurred to them as a result of their living in the community rather than as a result of their contact with each other.

DR. MITCHELL: One of your slides talks about the drug-related snorting, the snorting of drugs. I am not clear how that would transmit.

DR. ALTER: Neither is anyone else. There have been a couple of cross-sectional studies that have shown that individuals who are anti-HCV positive are more likely to give a history of snorting cocaine than are anti-HCV negative individuals.

at

We don't know whether that represents an independent mode of transmission such as through contaminated straws, has been one hypothesis, or whether that represents an individual who may also inject drugs but not admit to it.

At the moment, at least, I am not considering that as an independent risk factor for acquiring hepatitis C even though it has been shown to be a risk for being positive. I am not sure. The behavior, itself, is an independent mode of transmission.

DR. CANTILENA: I am Cathy Cantilena, if I could just add to that for a second. That was some data that actually came out of one of the studies that we did at NIH, Dr. Harvey Alter and myself. What we did identify was, in fact, that intranasal cocaine use was reported by, I believe, it was 68 percent of people who were truly hepatitis C positive. When we did a logistic regression analysis of the data, that, in fact, did turn out to be--at least, there was a statistical association that that was independently associated with HCV positivity.

But, as Miriam was saying, we are having a hard time, as if everyone else, trying to prove that, in fact, one can directly transmit hepatitis C virus through the act

at

of intranasal cocaine snorting and it is very difficult, and Harvey Alter and I have been around and around about this. How do you do that? It is hard to have monkeys doing this where it is a whole lot easier to have, actually, humans doing it.

But it is a difficult problem that we haven't found the correct scientific answer for yet.

DR. ALTER: We rarely find it among patients with newly acquired disease in the absence of any other risk factor. Although it was independent, that 68 percent included drug users, injection users. Do you know what percentage of the population that snorting cocaine was their only risk factor?

DR. CANTILENA: Miriam's question is a good one. We actually tried to sort that out. I don't know the number off the top of my head. I am not the mathematician, statistician, but when we went through the multivariate model it is still, independent of intravenous drug use, or was a risk, in fact, for HCV positivity in blood donors.

DR. ALTER: And I recognize that. I was just curious as to the proportion of positives that it accounted for all by itself.

DR. CANTILENA: Very few.

DR. ALTER: That's interesting.

at

DR. HOLLINGER: On the other hand, there are at least a couple of other studies which have looked at this. And when you really stop to think about it, even on the side, with patients who are snorting cocaine, nasal mucosa with the cocaine is very hyperemic, lots of vascularity there.

You could assume if you were going to pass a tube around or a dollar bill with cocaine in it and you pass it to the next person, that is not much different than injecting drugs, basically. So while it has been associated very much, I think there is some real potential there for cocaine.

I might also mention, much of Miriam's results are from acute cases. I might mention that, as distinct from hepatitis B, the highest concentrations of hepatitis B are often during the time when the ALT is elevated, the patients have virus at the time when they are acutely ill.

Then it may remain very high for long periods of time. But, for hepatitis C, often the very highest concentrations are before the patient is ill and then they are less as the patient has chronic disease. And so it maybe has something to do with transmission may be more likely in the acute phase than in the chronic phase on the basis of concentration of virus which we know is important

at

for B, C--that is, transmission by a nonparenteral route as distinct from a parenteral route.

So there are some other potentials there, too.

Any other questions?

Thanks, Miriam.

The next talk will be by Cathy Cantilena, testing of sexual partners. Cathy is from the NIH.

Testing of Sexual Partners

[Slide.]

DR. CANTILENA: Most hepatitis-C-virus-infected donors are found to have parenteral risk factors for hepatitis C virus exposure. However, unlike other blood-borne parenterally transmitted viruses such as hepatitis B virus and HIV, conflicting information, as we have just heard, exists as to the efficiency with which HCV is transmitted by the sexual route.

Today, what I hope to do is review some of the current information pertaining to the sexual transmission of HCV.

[Slide.]

It appears that the efficiency of HCV transmission through sexual contact is well below that for HBV or HIV. Although it is difficult to put a number on some of the reviews and the articles that have appeared, certain authors

at

have. Dr. Dienstag reviewed the literature and suggested the risk was low, perhaps on the order of 5 percent earlier this year at the NIH Consensus Conference on the management of hepatitis C.

Dr. Miriam Alter has found in her studies that were published in the early '90's that 10 percent of community-acquired HCV cases reported a sexual or household exposure to a known case.

In the next several slides, I will present some observations that have been made to support a role for sexual transmission of HCV. The last several slides I will show will demonstrate the opposite; that is, showing that there is little direct evidence for transmission of HCV.

[Slide.]

There have been a number of studies on risk factors for hepatitis C virus exposure. In the prospective study that involved blood donors that we conducted at NIH, we found five risk factors that were significantly associated with HCV infection in blood donors in a multivariate analysis.

Among 240 HCV-positive blood donors, confirmed by RIBA, intravenous drug use, transfusion, intranasal cocaine use, sexual promiscuity and ear piercing in men all were significantly associated with HCV positivity and HCV

at

infection.

Sexual promiscuity in our study was reported by 53Êpercent of those with HCV infection versus 24 percent of the controls. Our definition of sexual promiscuity was defined by a history of sexually transmitted disease, sex with a prostitute and five or more sexual partners per year.

Thus, a statistical association exists between sexually promiscuous behavior and HCV infection. In the same study of blood donors, we directly tested their sexual contacts and children. I will present that data in a few minutes.

[Slide.]

Other investigators identified rates of HCV infection in people with high-risk sexual contacts, rates which far exceed that seen in blood donors which is now about 0.2 percent in the U.S.

Dr. Weinstock and his colleagues studied patients attending a sexually-transmitted disease clinic and found HCV infection at a rate of 7.7 percent. Dr. Osmond studied individuals participating in a study of HIV transmission between men and women and found rates of 18 and 33 percent, respectively.

It is notable that in both of these studies, a risk factor of injection-drug use was elicited in a highly

at

significant proportion of the anti-HCV positive individuals. Blood transfusion and hemophilia were also associated with HCV positivity.

Measures of sexual behavior that were not associated with HCV positivity in these studies were sex with an IV drug user, sexually-transmitted disease, multiple partners and homosexually in addition to HIV-positive status in the second study.

These studies corroborate the importance of injection-drug use in blood transfusion in transmitting HCV and they underscore the importance of ascertaining parenteral exposures when examining the sexual transmission of HCV.

[Slide.]

Likewise, in studies of anti-HCV positivities in homosexual men, high rates of HCV infection are reported for those who had used parenteral drugs both in the U.S. and Spain. In contrast, in a non-IV-drug-using group of homosexual men, there are much lower rates of anti-HCV positivity on the order of 4 and 5 percent.

[Slide.]

This is the same study that Dr. Miriam Alter just reviewed for you just with a little bit of a different twist. He performed a study, as you have heard, of HCV

at

infection on patients attending sexually-transmitted diseases clinics in Baltimore. He found 309 sexual partners of 1,039 non-drug-using patients to test for anti-HCV.

As you heard earlier, 7 percent of the men and 4Êpercent of the women tested anti-HCV positive. Risk factors in the index case that were associated with the presence of HCV infection in the sexual partner were a young age, less than 28 years, more than 24 lifetime partners, HIV infection, trichomonas infection, cigarette smoking and a history of men who had had sex with men.

Thus, this study pointed towards sexual exposure as a potential risk for HCV infection in a group with frequent sexual contacts.

[Slide.]

Dr. Alter also referred a little earlier to a study that Dr. Akahane and his colleagues performed which was a widely cited point-prevalence study in Japan that presented some convincing data in support of sexual transmission of hepatitis C.

Spouses of 154 patients attending liver-disease clinics were screened for anti-HCV and excluded from study if they had reported a history of transfusions, premarital non-A/non-B hepatitis, injection drug use or extramarital affairs.

at

Anti-HCV was detected in 27 percent of the spouses and HCV RNA in 18 percent of the spouses which, in fact, of those, almost 90 percent of those were genotype identical to their partners. The frequency, as you heard earlier, of HCV infection increased with the duration of marriage. None of the spouses that were married less than ten years were anti-HCV positive versus 3 out of 5, or a striking 60 percent, of those couples who were married for more than 50 years.

This is of clinical importance because ten of the 24 infected spouses had biochemical or histological evidence of liver disease. These data suggested that sexual exposure to HCV increases over time during marriage. However, consideration should also be given to the possibility that covert parenteral exposures may be more likely in Japanese than in Western countries.

Other studies in Japan, which I am not going to review, where the prevalent of anti-HCV was as high as 20 percent, practices such as acupuncture and folk medicine, which is called vacuuming, often are performed with unsterilized shared instruments.

Vacuuming involves--I don't have a slide of this but it involves applying suction cups to muscles to relieve congestion of blood in those muscles in the area. These

at

practices might be engaged in by both spouses and other family members as well.

The data provided by Dr. Akahane did not provide information to exclude this possibility or to provide the prevalent rates in other non-sexual household contacts.

[Slide.]

Dr. Eyster and his colleagues compiled data on the prevalence of hepatitis C virus in sexual partners of hemophilia patients. He compared the frequency of transmission of HIV and HCV at ten hemophilia centers. The prevalence of HIV in sexual partners of 170 multitransfused HIV and HCV coinfected hemophiliacs was 12 percent while the transmission of HCV in the same group appeared to be about 4Êpercent.

This is in sharp contrast to the next group who were only infected with hepatitis C virus. As you can see here, none of their sexual partners acquired a hepatitis C virus infection. One might infer from this study that the transmission of HCV to sexual partners is favored by a high concentration of circulating HCV in the index case which is fostered by HIV infection.

The immunosuppressive impact of HIV infection is assumed to favor increased levels of HCV replication. This study supports the concept that, under most circumstances,

at

in cases of HCV infection alone, the efficiency of HCV sexual transmission is low.

[Slide.]

Dr. Brettler and his colleagues also set out to determine the prevalent of HCV infection in female partners of hemophilic males. He studied long-term sexual partners of 106 anti-HCV positive hemophiliacs from Europe, Asia and Australia. The sexual-partner cohort was tested for antibodies to HCV and HIV as well.

No sexual partner was acutely infected with hepatitis B virus, but six had anti-hepatitis-B core antibodies and four of 66 tests, or 6.2 percent, had anti-HIV antibodies.

Three of 66 that were tested had anti-HCV antibody that was confirmed by RIBA. One of these three partners was also anti-HIV positive. She reported that she was also a past sexual partner of an intravenous drug user but had denied intravenous drug use herself. Another sexual partner who was HCV positive was a nurse in a geriatric unit and the last one had had a history of transfusions in this group.

Since this study didn't show that HIV/HCV coinfection was likely to be associated with HCV transmission to the sexual partner since two of the three cases of anti-HCV positivity occurred in the absence of HIV.

at

Overall, the rate of HCV sexual transmission was small and may even be lower than it appears here because the females had a potential external source of HCV exposure.

[Slide.]

Support for the rarity of sexual transmission between stable, monogamous, partners derives from observations in sexual partners of women infected with HCV by contaminated anti-D immunoglobulin. In a German study, reported by Dr. Meisel, neither serologic nor virologic evidence was detected for HCV in any of 94 husbands of 160 HCV-infected women who had had hepatitis C virus infection since the late 1970s.

Only 3 of the children, all of whom were without clinical symptoms in this study, had anti-HCV antibodies. Similarly, among 392 long-term sexual partners of Irish women who had also gotten their hepatitis C virus infection from contaminated anti-D immunoglobulin in 1977, in this group, only 3 of the 393 partners tested were anti-HCV positive.

One of the three positive partners could not be confirmed with other serologic anti-HCV assays. One of the partners had been transfused and one of the partners, at the time that this data was reported had had no further follow up, so just one anti-HCV positive test.

at

Thus, what this shows is that after almost two decades of sexual activity in these cohorts, sexual transmission was either nonexistent or very low.

[Slide.]

Likewise, Dr. Everhart and colleague were unable to document any transmission of hepatitis C virus among 42Êsexual contacts of 44 patients with chronic non-A/non-B hepatitis at NIH after approximately four years of sexual contact. Even in three sexual partners in the study who had had repeatedly ALT elevations, anti-HCV could not be demonstrated.

Now, this anti-HCV was detected by radioimmunoassay and not EIA, so this could an underestimate and I don't think the EIAs have been repeated in this case.

[Slide.]

Dr. Bresters in the Netherlands looked for HCV infection among 50 heterosexual partners of HCV-infected individuals, a large proportion of whom were hemophiliac. He found no evidence of transmission after median sexual relationships of 13 years.

He also used the branch DNA assay to quantitate the amount of HCV RNA in the viremic-index subjects and found the median was similar to that of other hepatitis C virus-infected patient groups.

at

He proposed that the absence of transmission in his study was explained by the relatively low serum-HCR/RNA titers as compared to such viruses as hepatitis B or HIV which may be too low to allow for infectious hepatitis C virus doses to be spilled over into secretions.

[Slide.]

Getting back to the data from the hepatitis-C-virus-positive blood donor cohort which we follow at NIH, this represents an update of some of the data that was reported a couple of years ago now in the New England Journal of Medicine.

We have been able to test 108 sexual partners of 105 anti-HCV positive blood donors to date. Of this group, 16 of 108, or 14.8 percent, themselves and the sexual partners tested anti-HCV positive. There is not a single sexual partner among these individuals who does not report intravenous drug use or a history of transfusion. They all have a known external parenteral risk factor for hepatitis C virus infection.

Of the two children who were positive, of these RIBA positive hepatitis-C virus-infected blood donors, one was a multitransfused child and the other one was tested as a neonate and has no further follow up. You will note that also, among hepatitis C virus indeterminate and control

at

blood donors that no sexual partners or children were HCV-positive

Thus, among blood donors, the rate of hepatitis C virus positivity among their sexual partners may be explained by the sexual partner's independent risk factor for HCV infection rather than sexual transmission of the virus.

[Slide.]

This last slide of data summarizes some of the data that I have briefly reviewed which do not support the sexual transmission of HCV infection. After determining which sexual partners were positive and specifically looking for evidence for other routes of HCV exposure in all these studies, no sexual partner had hepatitis C virus infection that could not be accounted for on the basis of their sexual exposure alone.

In other words, all the sexual partners had other sources from which HCV infection might have been acquired except for the one husband in Ireland from Dr. Powers' study who had had no follow up.

So, in conclusion, the rate of HCV infection among homosexual men and people attending STD clinics, after correcting for the injection-drug use, is on the order of 5 to 8 percent, higher than that seen in U.S. blood donors but

at

lower than the rates of HBV and HIV that might be seen in high-risk populations.

Indirect evidence suggests that a higher viral concentration in an immunocompromised test could permit sexual transmission. In areas of high endemicity, where spouses may be more often mutually infected, covert parenteral exposures may play a role in sexual transmission.

[Slide.]

Lastly, after correcting for other potential exposure to HCV in many studies, little direct evidence exists for the sexual transmission of HCV between partners. To reconcile which seems to be widely divergent data, one must conclude that the sexual transmission of HCV is possible but uncommon.

That's it. Thank you.

DR. HOLLINGER: Thank you.

Any questions? If not, we will go to the last speaker, Sherri Stuver, from the Harvard School of Public Health who will speak on HCV infection within married couples in Japan.

HCV Infection Within Married Couples in Japan

DR. STUVER: Thank you. I apologize to the committee that I didn't get copies of my slides to you ahead of time. I hope that you will be able to follow along

at

anyway.

[Slide.]

The data that I will be presenting today was collected in conjunction with the Miyazaki cohort study which is a prospective follow-up study of human t-lymphotropic virus type 1 and hepatitis C virus infections in Miyazaki Japan.

[Slide.]

The Miyazaki cohort study was established as a collaborative effort between the Harvard School of Public Health in Boston and the Miyazaki Medical School in Japan. Recently, as we have begun studying HCV in our cohort, we also have been working with Dr. Edward Tabor at the Division of Transfusion Transmitted Diseases.

[Slide.]

The Miyazaki cohort study is a community-based study that involves residents of two small villages in Miyazaki prefecture. The study has been ongoing since November of 1984. Enrolled subjects attend free government-sponsored annual health examinations that are targeted to village residents who are 40 years of age or older.

These health screenings involve a physician examination as well as other routine health procedures and

at

tests. A blood sample is also collected and stored for each subject and written questionnaires are used to collect data on basic demographic and health history information.

As of April of 1997, nearly 2,000 subjects had been enrolled into the cohort through 13 screens. The median age at baseline enrollment is 55 years.

[Slide.]

This is a picture from one of the study villages. You can see this is a fairly rural area. The primary occupation is farming although some fishing is also done.

[Slide.]

This is a typical community center where the health screenings would take place.

[Slide.]

The Miyazaki cohort study was initiated to study the natural history of human t-lymphotropic virus type 1, or HTLV1, infection in a highly endemic population. The baseline HTLV1 seroprevalence is about 26 percent among cohort subjects.

HTLV1, which can be transmitted through several different routes, is associated with a number of very important disease outcomes. In 1994, a pilot study of the cohort revealed an almost equally high prevalent of anti-HCV positivity in one of the study villages. So we have a new

at

goal in our cohort which is to investigate the natural history of HCV in this particular study village which we call village A where the seroprevalence of anti-HCV is about 23 percent at baseline.

There are 987 cohort subjects in this particular village among whom we have observed nine liver-cancer deaths. Six of these were confirmed to be anti-HCV seropositive. A seventh was also anti-HCV positive but we had insufficient serum on that particular subject to do additional confirmatory testing.

[Slide.]

In collaboration with Keitaro Tanaka at Kyushu University, we decided to perform a cross-sectional study of married couples within the cohort in order to determine the role of heterosexual transmission of HCV within this population.

[Slide.]

The subset of subjects that were studied were those village A couples who attended screen 8 which occurred in November of 1981. In the study, we assessed HCV serology by using the stored serosamples that we had from these couples. Anti-HCV was detected by a second-generation immunoradiometric assay with confirmation of the positives by RIBA.

at

The presence of HCV RNA was also determined using nested RT-PCR. Those individuals who were negative by that test were also retested using the Amplicor HCV assay. Among the subjects who had HCV RNA, we also looked at what their HCV genotype was using a PCR method that had four genotype-specific primers.

[Slide.]

The 109 couples that were studied had the following anti-HCV positive concordance. For 14 of the couples, both of the spouses were positive for anti-HCV. In 13 couples, the husband alone was positive. In 21 couples, only the wife was positive for anti-HCV. In the remaining 61 couples, neither of the spouses were positive.

So, based on this distribution, then, a spouse was about twice as likely to be anti-HCV positive if his or her partner was also anti-HCV positive than if the partner was anti-HCV negative. We made this estimate by comparing, for example, the proportion of wives who were positive that were married to anti-HCV positive husbands to the proportion of wives that were positive that were married to anti-HCV negative husbands.

Then we did the same thing for the husbands and it comes out to be about 2 for both partners. Although this is statistically significant, this association is actually

at

smaller than what we have seen for the correlation of HTLV1 infection within married partners in our cohort where the association has been more like five to seven-fold.

[Slide.]

This is a table summarizing these couples' characteristics according to the concordance of anti-HCV within the couples. So these are the different groups. There were no significant differences across the serostatus groups with respect to the husband's age, the couple's length of marriage, the wife's number of pregnancies or the proportion who reported ever having used barrier contraception.

We looked at the presence of HCV RNA in both partners in those couple where at least one of the partners was anti-HCV positive, so in both partners in the concordantly infected than in both of the discordantly infected groups.

In the discordantly infected couples, none of the anti-HCV negative spouses had detectable HCV RNA in their serum. Also, among the anti-HCV positive spouses, the presence of HCV RNA was not associated with an increased likelihood that their partner would have anti-HCV. So that would be comparing the RNA status of the husbands by whether or not the wife had anti-HCV and comparing the RNA status of

at

the wives by whether or not the husband had anti-HCV.

Assuming that HCV RNA would be a marker of increased infectiousness, one might have expected that the presence of HCV RNA in on partner might predict anti-HCV seropositivity in the other partner if sexual transmission was occurring within these married couples. However, in these data, we did not see such an association.

Moreover, in the six couples where both partners were positive for HCV RNA, only 50 percent of them had, in fact, the same HCV genotype so even though there was a significant correlation of anti-HCV status within these married couples, it is not readily apparent that sexual transmission played a major role in the observed concordance.

Now, these findings, of course, are going to be limited by the fact that they are cross-sectional. However, we do have some preliminary data from prospective follow up of the subjects in village A. This is why I didn't get these slides to you beforehand. I was still doing these calculations early this week.

So we have done testing of the baseline in more recent sera of the village A subjects for the presence of anti-HCV. The screening assay that we use is a second-generation HCV particle agglutination assay which is

at

an established assay in Japan.

Confirmation of the positives was done using their RIBA 2.0 test. We have identified 14 anti-HCV seroconverters which represent 2.5 percent of the 559 anti-HCV seronegative subjects who have attended at least two or more of the annual health screenings. So the incidence rate of anti-HCV seroconversion is estimated to be 3.6 per 100,000 person years in this population.

Six of the seroconverters were males. Eight of the seroconverters were females. We have done additional testing of the sequential samples of the seroconverters for anti-HCV as well as for HCV RNA and for HCV antigen. The latter test was developed in Japan and is based on monoclonal antibodies against recombinant HCV core protein.

[Slide.]

In fact, one of the seroconverters, we found, did have detectable HCV RNA at the screen one year prior to the one at which he became anti-HCV seropositive. With regard to risk factors for transmission, we do suspect that one of the seroconverters may have acquired his infection from a blood transfusion which he reported having received in the year prior to his first anti-HCV positive specimen.

In addition, five of the eleven seroconverters who have spouses that are enrolled in the cohort have a spouse

at

who is anti-HCV seropositive. So this is 45, nearly 46, percent of those particular seroconverters. It is 50 percent among the male seroconverters and 43 percent among the female seroconverters.

Of the five anti-HCV seronegative spouses of the seroconverters that were tested, none of them had HCV RNA.

[Slide.]

So based on the available data, prospective data, on all couples in village A, the risk of acquiring HCV infection among husbands is 5.3 percent if their wife is anti-HCV seropositive versus 1.4 percent if their wife is anti-HCV seronegative, so this is a nearly four-fold increased risk although you can see that the relative risk was not statistically significant.

Among the wives, the risk of seroconversion, anti-HCV seroconversion, was 7.3 percent if the husband was anti-HCV seropositive and 2.5 percent if he was not. Again, this threefold increased risk among the wives, given that their husband was anti-HCV seropositive, was not statistically significant.

Again, it is interesting to note that, with respect to HTLV1 infection in the cohort, the relative risk of seroconverting to HTLV1, given that you have a spouse that is an HTLV1 carrier, is much higher than what we see

at

here for HCV, on the order of a relative risk of 25.

[Slide.]

This is a table of some viral markers that were measured among the five seroconverters who were married to anti-HCV seropositive spouses. So this is the data for both spouses for the seroconverter, the CV, and then for that seroconverter's spouse.

Really, the basic point that I wanted to make here is that for two of the four spouses, or 50 percent of the spouses, who were tested for HCV RNA, they had HCV RNA present in their serum, which is a similar proportion to what we saw in the cross-sectional analysis of married couples in the concordantly anti-HCV seropositive couples.

However, you can see that, for couple 3, when we looked at the genotype that each of these spouses carried, it was, in fact, different being type 2B for the seroconverter and type 1B for the wife, suggesting that sexual transmission was unlikely to have played a role in the transmission of the virus within this couple.

[Slide.]

In summary, then, based on the HCV seroconverters' data, heterosexual transmission appears to account for fewer than half of the new HCV infections in this population. Also, based on the seroconverter data and the data from the

at

married couples cross-sectional analysis, heterosexual transmission unlikely explains completely the clustering of anti-HCV positivity within couples in this older endemic community-based population in Japan.

This is basically what you have been hearing from the previous two speakers, that the clustering within endemic areas in Japan likely is due to other shared environmental factors that they have experienced, either mass vaccinations or other medical procedures or other folk remedies that are in the area and not as much is likely due to actual sexual transmission of the virus within those couples.

Thank you.

DR. HOLLINGER: Thank you.

Are there some questions?

DR. ALTER: Although this doesn't really have a bearing on the overall conclusions from the study, I have a question about the genotyping and the method of genotyping as well as the findings of the five couples who were RNA positive. First, you mentioned that sequencing was done in the core region to determine genotyping.

DR. STUVER: That's correct. That is the method that they use in Japan. It is Okomoto's paper.

DR. ALTER: My question is don't you need, for

at

subtyping, NS5B to determine the subtype even with the Okomoto method?

DR. HOLLINGER: I don't know if Okomoto uses it or not. Some do and some don't. Some don't use the NS5.

DR. ALTER: And they can still determine the subtype?

DR. HOLLINGER: It would be useful to use it.

DR. ALTER: I guess my second question has to do with--Japan, just like most other countries, has a predominant genotype circulating in the population. I am wondering if you think it is unusual that, among six couples, or five or six couples, half of them would have a different genotype not because they are related or unrelated to each other, but just because you would expect the majority to have the predominant genotype in the population.

DR. STUVER: Right. I don't think that it is unusual that it is 50 percent by chance alone because, at least in this particular population, the predominate, like, two thirds when we have done the genotype testing are type 1B and then the other, about a third, is type 2B. So by chance alone, that combination would give you about 50 percent.

So it is about what you would expect by chance alone.

at

DR. ALTER: Good. Thank you.

DR. HOLLINGER: Any other questions from the committee or anyone from the audience? There was no one who stated that they wanted to speak but if there is someone in the audience that has something that they would want to say, feel free to do so.

DR. NELSON: I have forgotten. What did you say was the overall population prevalence of hepatitis C in this community, in this village?

DR. STUVER: It is about 23 percent at baseline of all of cohort subjects in that village.

DR. HOLLINGER: The relationship to HTLV1?

DR. STUVER: I haven't looked at that yet among the couples. We do have some other preliminary analysis where we are looking at the effect of HTLV1 as far as disease outcome. Although in the married couples cross-sectional study, HTLV1 did not seem to be strongly associated with hepatitis C anti-HCV serostatus.

Certainly, HTLV1, the seroconversions that we have are predominately, we believe, due to sexual transmission within the married couples so there is much more sexual transmission of HTLV1 than there appears to be for HCV.

DR. NELSON: I was just going to ask about barrier contraceptives like condom use, are frequently used for

at

contraception, I guess, but the implication of your previous study is that it is used less often enough that HTLV1 is transmitted.

What about other STDs in this? Do we know anything about that?

DR. STUVER: The one thing we need to remember is that this is an older population, primarily past reproductive age. So the information on barrier contraception is going to be historical information, and where that fits as far as when HCV was introduced into the population.

But there wasn't really a difference in the cross-sectional study as far as the proportion that had reported ever having used it in the past.

We also, in that study, measured antibody to the Treponema syphilis, the agent of syphilis. Again, we didn't see any relationship with anti-HCV positive serostatus among those couples which, again, would be evidence against that HCV is being transmitted sexually within this particular population.

DR. HOLLINGER: You mentioned that they have a very high prevalence of HCV in this population and suggest a cohort effect of some sort which also could be a similar possibility in the Akahane study which looked at people who

at

had been married for less then ten years versus 50 to 60. That is maybe just a cohort effect and had nothing to do with their marriage.

The other issue, though, is I have frequently heard in Japan, I have never been really to really able document it although I have talked to several people over there. It was my understanding that until about the 1970's or 1980's, maybe as late as the 80's, that many children were vaccinated using the same needle.

They were sort of lined up and just vaccinated down the line for their vaccinations. I have had Japanese colleagues who have told me that but I have never been to document it that this really took place. Does anybody have information on that?

That was one of the reasons that was said was a possibility of why they have so much hepatitis C or other things in that population. Do you know Kenrad?

DR. NELSON: I don't know. I spent a day with a group from Egypt which has an even more rampant hepatitis C epidemic or population prevalence than Japan. In fact, in males 40 to 60 or something, the rate are, like, 60 percent are positive for hepatitis C.

The hypothesis there is that it was related to the Schistosomiasis program which used frequent parenteral

at

injections and Egypt was one of the countries in the Middle East that had medical-care money, et cetera, but not much attention given to needles.

But you would think that, in that setting, a high prevalence, in fact, where there was a cohort might be a good place to study sexual transmission because the rates would be high enough in people who are not constantly using needles.

That is the problem disentangling it in the U.S. You go to an SD clinic and there is a lot of drug use and unreported drug use may overwhelm sexual transmission. But I think Egypt and places like that there should be more careful studies of sexual transmission.

DR. HOLLINGER: Even in this country, there is a lot of covert potential parenteral sources. As you know, In Miami, many of the Hispanic children, the families would give them inoculations, vitamins, as small children on their own in the family situation as potential sources. We don't think of things like prematurity which is a question I ask many of my patients.

As you know, about 60 or 70 percent of newborn infants who are premature receive blood infusions. Many years ago, it was with multiple donors. Nowadays, when they do it, at least they use the same donor and sort of retain

at

that blood for use.

So there is another potential source that one has to think of. People are not very willing to give parenteral exposure information. I had a patient the other day who called--when I saw him the second time, he said that he didn't really tell me the first time he had used drugs. One of the reasons he didn't was because he was afraid it might make a difference whether he would get a liver transplant.

So there are a lot of reasons why people don't indicate that information.

Any other questions from the committee?

DR. HOLMBERG: One of the previous speakers had made mention that the Japanese study had correlation with the seroconversion in relationship to the duration of the marriage. But I didn't see that in your slide there.

DR. STUVER: This isn't that study. We, in fact, didn't see, in the cross-sectional study, any difference in length of marriage according to whether the couple was both infected or just one partner was infected or neither partner was infected.

We saw no difference as far as length of marriage.

DR. HOLLINGER: But this was an older population, anyway, wasn't it?

DR. STUVER: Yes; it is not going to have that

at

same spread of years of marriage. It was the Akahane study that showed that relationship between duration of marriage and anti-HCV seropositivity, although I think another Japanese study has also--one in Taiwan, Kayo's study. But we didn't see it in our particular population.

DR. HOLLINGER: I want to thank the speakers for this afternoon also for providing this update to the committee.

If there are no further--oh; do you have something?

DR. SMALLWOOD: I would just like to announce that the next Blood Products Advisory Committee is tentatively scheduled for March 12 and 13, I believe Thursday and Friday. The site is yet to be determined, but if you contact our offices and look at the Federal Register notice, that information will be made available to you.

Thank you.

DR. HOLLINGER: Thank you. Thank you all.

[Whereupon, at 2:36 p.m., the proceedings were adjourned.]